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ESTD.
Flexible control and training of posterior alpha-band Oscillations
2015
– JÖRN M. HORSCHIG –
DONDERS
series

Flexible control and training of posterior alpha-band oscillations

Jörn M. Horschig

The research presented in this thesis was carried out at the Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging of the Radboud University Nijmegen, the Netherlands, with financial support from the research program "The healthy brain" funded by the Netherlands Initiative Brain and Cognition (NIHC), a part of the Organization for Scientific Research (NWO) under grant numbers 056-14-011 to prof. dr. Ole Jensen.

Printed by GVO drukkers vormgevers, www.proefschriften.nl

Cover page idea by Jörn M. Horschig
Design by Stefan Kuhnigk, www.kuhnigk.com

ISBN 978-94-6284-020-1
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Flexible control and training of
posterior alpha-band oscillations

Proefschrift

ter verkrijging van de graad van doctor

aan de Radboud Universiteit Nijmegen

op gezag van de rector magnificus prof. dr. Th.L.M. Engelen,

volgends besluit van het college van decanen

in het openbaar te verdedigen op maandag 8 juni 2015

om 12.30 uur precies

door

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geboren op 30 januari 1985

te Kleve, Duitsland

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Summary

There is increasing evidence that ongoing neuronal oscillations can be directly related to cognitive performance in humans. For example, the performance in visual attention tasks is strongly related to the distribution of posterior alpha-band oscillations, which allow inhibiting task irrelevant information. In daily life attentional demands have to be flexibly adjusted to the environment. Improving the ability to flexiblyadjust attention to environmental demands is therefore crucial. Here, I first demonstrate that the statistical properties of the environment have consequences for how individuals adjust their posterior alpha activity; supposedly this reflects the environment-dependent allocation of attention. Further I show that some participants were better at adjusting to the environment than others and that this trait was reflected by the ability to modulate the alpha activity. Next I ask if the ability to modulate the posterior alpha activity can be trained and to what extend this training has consequences for behavior. To this end I have developed an MEG based brain-computer interface (BCI) controlled by posterior alpha activity. Participants could gain control of this BCI by allocating their spatial attention within a single session, and became better in following sessions. In a subsequent experiment, this setup is used to train the posterior alpha activity. As a consequence of the training, behavioral performance in a visuospatial attention task was modulated. Finally, I investigate the role of the frontostriatal system in the control of oscillatory brain activity, and show how alpha oscillations are involved frontostriatal communication. In sum I show in this thesis that posterior alpha oscillations can flexibly be adjusted to current attentional demands. Further this ability can be improved by training posterior alpha oscillations using brain-computer interfacing. This suggests that posterior alpha oscillations play a causal role for the allocation of spatial attention and that BCI training of neuronal oscillations can be used to augment human cognition.

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Chapter 1

Introduction

Imagine that you are waiting in front of a traffic light for the green light. A traffic light (see Figure 1) is specifically designed to trigger exogenous attention processes. A bright light changes location and color, thereby drawing your attention in a bottom-up fashion. Despite the saliency of the upcoming change in your visual field, you are attending exclusively to it and ignoring the surrounding environment. You could decide to rather attend to the red Ferrari at the nearby parking lot. However, if your current main priority is to get to your destination as fast as possible, you should better not waste time by being distracted from the traffic light for a single moment. You consciously ignore everything BUT the traffic light to improve your reaction time when the light turns green. This latter part of attention has been described as endogenous or top-down control of attention. In contrast to the automatic bottom-up attention processes, you can consciously modulate the amount of attentional top-down control.

Figure 1. A traffic light that turned yellow – or orange, depending on what language you are speaking (Mitterer et al., 2009). Despite the salient change in color and location when turning green you are additionally ignoring everything else in order to optimize your reaction time.

Exogenous here means the influences of the outside world. You perceive the traffic light, and upon a change in visual stimulation, i.e. color and location of the light, your brain networks get notified that something has happened. This notification is an automatic process – a process crucial for survival. As humans we were evolutionary shaped over millennia to adhere

to such exogenous changes in the environment and make use of it. Exogenous attention is in contrast to *endogenous* attention. A number of events are happening around us. However, we are able to focus on only the most behavioral important event, or in other words we are able to *ignore everything BUT the traffic light*. This is a pro-active process that requires effort. You need to actively attend to the traffic light, and actively prevent yourself from attending somewhere else. While in daily life this happens frequently and automatic, it is an effortful process and a vast number of times this fails, mostly when something unexpected happens. For example when a squirrel hops by the window of your car you are likely to make a saccadic eye movement towards the squirrel – just a short look. Again, this failure is evolutionary important: if the squirrel had been a carnivorous creature, like a velociraptor[1], you would appreciate the automated notification of this exogenous attention process.

The terms exogenous and endogenous go hand in hand with the terms bottom-up and top-down, which describe these processes in hierarchical terms. A top-down process describes the delegation of responsibilities from a higher order brain region to a lower order brain region. A lower order region is supposed to receive raw, unprocessed information, whereas a higher order region receives already processed information and interprets this information further. An example in attention processes is the active inhibition of brain regions that process behaviorally irrelevant information, and the active promotion of brain regions that process behavioral relevant information. Thus while you are waiting for the green light, a top-down process facilitates brain regions that process the color green. Also, your spatial attention system will suppress information coming from other locations than from the traffic light to prevent that information from being further processed. Higher order regions thus only receive those pieces of information that are necessary for the task at hand. You might therefore miss *the red Ferrari in the nearby parking lot* – such a shame.

1.1 Covert visual spatial attention

During visual spatial attention you mostly make saccadic eye movements to the locus of attention. That way the center of your retina, the fovea, fixates what you are most interested in: the traffic light. In the fovea, spatial resolution is highest in daylight; therefore it makes sense to look at where you

[1] **A velociraptor is of course unlikely to appear – everybody knows that velociraptors live in Asia, not in Europe.**

lution is highest in daylight; therefore it makes sense to look at where you are attending to (see Gazzaniga, 2008). In contrast to this overt visual spatial attention, you can also attend to a different spatial location than you are currently looking to. This is called covert visual spatial attention, or in short, covert attention (Posner, 1980). For example, while waiting for the green light, your life partner might start talking to you and urge you to look at his/her face while talking to you. Nonetheless, you might covertly attend to the traffic light instead, because you consider a swift start upon the green light more important than analyzing his or her emotional facial expression.

1.2 The human visual system, and top-down and bottom-up visual attention networks

The visual system in the human brain is rather complex. Visual input first arrives at the eyes. Photoreceptor cells convert photons from the incoming light into electrical signals that are then transmitted further to the brain: visual information is transmitted via the optic chiasm to the lateral geniculate nucleus (LGN) in the thalamus and from there to the visual cortex (see e.g. Gazzaniga, 2008) and to other subcortical areas like the superior colliculus (see e.g. Boehnke and Munoz, 2008). The optic chiasm combines information from both eyes in a hemifield-specific manner: the left visual field of both eyes is combined and sent via the LGN to the right visual cortex, and the right visual field of both eyes is combined and sent via the LGN to the left visual cortex. The visual cortex constitutes the main cortical input layer of visual information where visual information is processed and sent to higher order visual regions. The visual cortex also receives recurrent connections from higher order visual regions, thus updates visual information by the outcome of the processing in higher order visual regions.

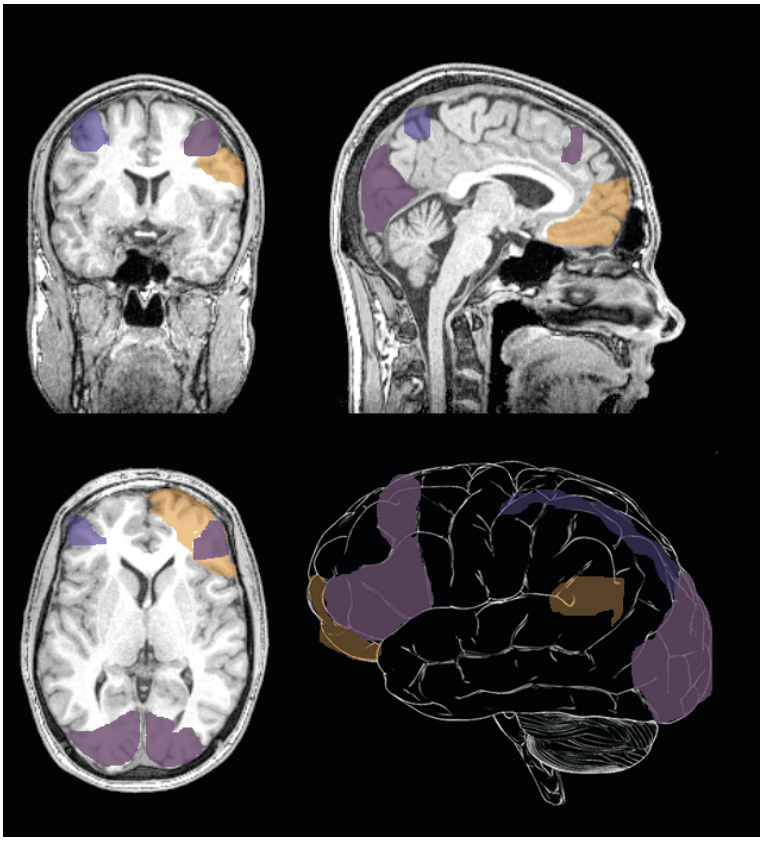


Figure 2 Schematic illustration of the dorsal (top-down) attention network (in dark blue) and ventral (bottom-up) attention network (in orange). Overlapping brain regions are marked in purple. Upper right: coronal slice. Upper left: saggital slice. Lower left: horizontal slice. Lower right: schematic illustration of the neocortex. The dorsal attention network consists of left and right frontal eye fields (FEF), left and right intraparietal sulci (IPS), right medial frontal gyrus, and visual areas. The ventral attention network consists of visual areas, right tempo-parietal junction, right ventral frontal cortex, right medial frontal gyrus, right FEF, right IPS and visual areas (Corbetta et al., 2008; Corbetta and Shulman, 2002).

The classical distinction between top-down (exogenous) and bottom-up (endogenous) attention processes is also reflected in the classical distinction between two attention networks in the human brain: the *dorsal attention network*, centered around the dorsal posterior parietal cortex (in particular the *intraparietal sulcus*, IPS) and the frontal cortex (including the *frontal eye fields*, FEF), and the *ventral attention network*, centered around right tempo-parietal and ventral frontal cortex (Corbetta et al., 2008; Corbetta and Shulman, 2002), see Figure 2 for a schematic overview. Whereas the dorsal attention network is responsible for the endogenous selection of sensory information (top-down processing), the ventral atten-

tion network is responsible for exogenous processes, i.e. the detection of behaviorally salient events (bottom-up processing). But also subcortical networks are involved in processing of visual information, for example the superior colliculus (Boehnke and Munoz, 2008; Comoli et al., 2003) or the pulvinar nucleus of the thalamus (Petersen et al., 1987; Saalmann et al., 2012; Saalmann and Kastner, 2011). Also the striatum is directly involved in detection of changes in the visual field (van Schouwenburg et al., 2010) and actively modulates the amount of frontoparietal connectivity (van Schouwenburg et al., 2013).

Box 1: Measuring electrophysiological neuronal activity

Brain processes can be investigated on various levels using several techniques, for example studying the firing pattern of single neurons. Different techniques need to be applied when studying brain networks, where the contribution of a single neuron is too marginal to affect network dynamics. In contrast, we require techniques to measure network activity directly. Among the various existing techniques, this thesis concerns electrophysiological techniques, which measure electrical properties of neuronal activity.

In this thesis two electrophysiological techniques will be used. The first technique is called magnetoencephalography (MEG) and measures the magnetic field resulting from the primary electric field that is produced by postsynaptic potentials (Cohen, 1968; Hämäläinen et al., 1993; Hansen et al., 2010). Magnetic fields resulting from the postsynaptic potentials are extremely small, thus only concurrent, synchronized activity can be measured. MEG measurements take place in a magnetically shielded environment to reduce environmental electromagnetic noise. In order to increase signal quality and signal-to-noise ratio even more, MEG makes use of superconducting signal transmission, which can be achieved by liquid helium. MEG is an extracranial measurement technique, i.e. the sensors are located outside of the human skull.

The second technique is called electroencephalography (EEG) and measures the electric fields of the secondary current that is produced by the postsynaptic potentials. These currents are also called return or volume current. Extracranial EEG describes the technique where electrodes are attached at the scalp, and the electrical field is measured outside the skull. Intracranial EEG describes the technique where electrodes are placed under the skull, at the cortex or in subcortical regions. In humans this is only for purely clinical reasons.

1.3 Covert visual attention networks in the human brain

Due to the transmission of visual input from the retina via the optic chiasm to the visual cortex, the right visual field is processed in the left visual cortex, and the left visual field is processed in the right visual cortex. During covert attention this hemisphere specificity is maintained so that attended visual information is processed predominantly in the contralateral hemisphere in early visual areas (Gitelman et al., 1999; Perry and Zeki, 2000; Worden et al., 2000). Furthermore, it has been shown that the degree of covert attention is disturbed by inducing magnetic pulses in the FEF and IPS, indicating that the dorsal attention network is directly involved in the top-down control of covert attention (Capotosto et al., 2012a, 2012b, 2009;

Box 2: Quantification of neuronal activity

Electrophysiological measurements of neuronal ensembles require a large cohort of neurons to be synchronously active. Mutual interactions of different types of neurons result in synchronous, rhythmic patterns producing so-called neuronal oscillations. By temporally adjusting their firing pattern to each other, neuronal assemblies can thereby form functional cohorts. Such dynamic interactions can also provide a flexible mechanism for interregional neuronal interactions (Fries, 2005; Varela et al., 2001).

Oscillations have three key characteristics. First, oscillations are defined by their specific frequency, the number of oscillations per second. In this dissertation, I will discuss two major frequency bands for neuronal oscillations: theta oscillations between 4 Hz and 7 Hz and alpha oscillations between 8 Hz and 14 Hz. Second, due to their rhythmic nature, the momentary phase of the oscillation is of crucial importance. Third, oscillations are most often characterized by their amplitude or power. These three quantities can be obtained by a Fourier transformation. The Fourier transformation $\hat{f}(\omega)$ of the time-domain signal $f(t)$ is a function of frequency, and yields as well amplitude as phase of the frequency, and is defined as:

$$\hat{f}(\omega) = \int_{-\infty}^{+\infty} f(t) e^{-i\omega t} dt$$

with $\omega = 2\pi f$ with f as the frequency of interest. The Fourier transformation yields Fourier coefficients, which are essential to compute functional connectivity measures like coherence and Granger causality. If two signals are coherent, their phase relation stays constant across time for a given frequency-band. Coherence is bound between 0 and 1, where 1 indicates full coherence, i.e. a stable phase relation for that frequency, and 0 indicates no phase coherence, i.e. no stable, i.e. a completely random phase relation for that frequency. Granger causality quantifies how much a signal contributes to predicting another signal. Granger causality also has a lower bound of 0, which indicates complete independence of the two signals. However, Granger causality does not have an upper bound. In contrast to coherence, Granger causality indicates directional influence from one signal to another, and is thus an asymmetric measure.

Romei et al., 2010). In addition to the dorsal attention network, another network consisting of parts of the basal ganglia, which includes the striatum, thalamus and cingulate cortex is also active during covert attention processes (Gitelman et al., 1999). Thus, different brain networks are active during the demanding task of covert attention, and it is likely that they are interacting with one another.

1.4 Neuronal Oscillations as a neural correlate of attention processes

Neuronal oscillations (see Box 2) represent fundamental functions of the human brain, where different frequency bands seem to be involved in different, partly overlapping processes (Buzsáki and Draguhn, 2004). This thesis mostly concerns alpha-band oscillations, usually defined as the frequency band between 8 and 14 Hz. For a long time, alpha-band oscillations have been thought to represent an idling state of the human brain (Adrian and Matthews, 1934; Berger, 1929). Recently, however, it has been hypothesized that alpha oscillations play an important functional role by inhibiting task irrelevant brain regions (Foxe and Snyder, 2011; Fu et al., 2001; Jensen and Mazaheri, 2010; Klimesch, 1999a; Klimesch et al., 2007). For example, during covert attention the ipsilateral occipito-parietal cortex processes the unattended visual field and exhibits high alpha power. This is supposed to represent the functional inhibition of this task irrelevant region. In contrast, the contralateral hemisphere shows low alpha power, representing functional disinhibition and allowing for processing of visual information. A general key characteristic of alpha oscillations is that they are anticipatory, i.e. this alpha-band hemispheric lateralization is evident before the onset of visual stimulation (Worden et al., 2000). Most importantly, a multitude of studies have found strong correlations between the quality of processing of the upcoming visual stimulation and the degree of alpha-band lateralization within individuals (Kelly et al., 2009; Thut et al., 2006), indicating that posterior alpha-oscillations are a reliable neural correlate visuo-spatial attention. However, the strength of posterior alpha lateralization differs among individuals, and correlates with the ability to ignore the unattended hemifield (Händel et al., 2011; ter Huurne et al., 2013). Theta-band oscillations are defined between 4 and 7 Hz and are mostly hypothesized to represent a neuronal correlate of the working brain, i.e. internal processing of information (Kahana et al., 2001; Klimesch, 1999a). I discuss properties of theta-oscillations as well as further characteristics of alpha-band oscillations in more detail in the individual chapters, and more generally in **Chapter 5.2**.

1.5 Main hypotheses and general outline of the thesis

The main goal of this thesis to investigate how posterior alpha-oscillations are modulated by attention and whether they can be attributed a causal role for the mechanism responsible in attention. In daily life, attentional demands constantly change and we have to flexibly adapt to them. Posterior alpha-band oscillations are supposed to reflect the allocation of visuospatial attention (see **Chapter 1.4**). In **Chapter 2** I ask in a covert attention task whether adjusting the degree of posterior alpha lateralization to environmental statistics predicts behavioral performance. Large individual differences in the ability to modulate the degree of posterior alpha lateralization have been found in other studies (Händel et al., 2011; ter Huurne et al., 2013). Therefore I also investigate individual differences in adjusting to environmental task demands, and investigate if the individual differences are reflected by posterior alpha-band oscillations as well. In light of this idea, I ask whether the ability to modulate posterior alpha lateralization can be trained using MEG brain-computer interfacing (BCI; see Box 2 for MEG and Box 3 for BCI) in **Chapter 3**. Subsequently, I ask whether the training to modulate the posterior alpha lateralization brings along changes in behavioral performance in a covert attention task in **Chapter 4**. If this turns out to be successful, it would allow to attribute a causal role of posterior alpha oscillations to cognitive processes in a similar vein as interventional studies using transcranial magnetic stimulation (TMS) recently did (Romei et al., 2010; Sauseng et al., 2011). Following up on this idea, I review and discuss how BCI or TMS paradigms can be used to investigate the causal involvement of other neuronal oscillations in different areas of cognition in **Chapter 5**. I also discuss the applicability of such paradigms in other target groups, which can potentially lead to new ways to treat neuropathological disorders. Finally, I investigate what brain networks are involved in controlling and modulating the posterior alpha rhythm. Here, the striatum might play a crucial, yet underestimated role. Recent evidence suggests that the striatum is directly involved in detection of behaviorally relevant, visual stimuli and directly controls the amount of frontoparietal connectivity (van Schouwenburg et al., 2013, 2010). In **Chapter 6**, I present a study in which brain activity was recorded from intracranial electrodes in a group of patients, while simultaneously recording the scalp EEG (for EEG recording techniques see Box 2). Here, I specifically investigate whether the ventral striatum is functionally coupled to frontal and parietal sites, both in anticipation of visual stimulation and during processing of visual information in the theta- and alpha-band. Finally in **Chapter 7**, I discuss the

broader implications of the here presented work and propose a number of future directions following up on my research.

Box 3: Brain-computer interfacing and neurofeedback

Brain-computer interfacing (BCI) refers to the technique to use an aspect of measured brain activity to control feedback typically presented on a computer screen (Wolpaw et al., 1991). An original goal of BCI is to create a mean of communication for paralyzed patients (Birbaumer and Cohen, 2007; Wolpaw et al., 2002). Neurofeedback refers to a related technique with a different goal: a participant receives direct feedback on the level of some aspect of brain activity and learns to consciously up- and down regulate that activity. Neurofeedback was originally mostly used to reduce clinical symptoms in ADHD and epilepsy patients (Sterman, 1973) or ADHD patients (Lubar and Lubar, 1984). Recently, it has been proposed to use BCI or neurofeedback techniques as a tool in empirical studies on cognitive neuroscience to test strong, functional hypotheses (Jensen et al., 2011, see also Chapter 5).

Chapter 2

Alpha activity reflects individual abilities to adapt to the environment

This chapter is based on

Horschig, J.M., Jensen, O., van Schouwenburg, M.R., Cools, R, Bonnefond, M. (2014) Alpha activity reflects individual abilities to adapt to the environment. NeuroImage 89, 235-243. doi:10.1016/j.neuroimage.2013.12.018

Abstract

Recent findings suggest that oscillatory alpha activity (7–13 Hz) is associated with functional inhibition of sensory regions by filtering incoming information. Accordingly the alpha power in visual regions varies in anticipation of upcoming, predictable stimuli which has consequences for visual processing and subsequent behavior. In covert spatial attention studies it has been demonstrated that performance correlates with the adaptation of alpha power in response to explicit spatial cueing. However it remains unknown whether such an adaptation also occurs in response to implicit statistical properties of a task. In a covert attention switching paradigm, we here show evidence that individuals differ on how they adapt to implicit statistical properties of the task. Subjects whose behavioral performance reflects the implicit change in switch trial likelihood show strong adjustment of anticipatory alpha power lateralization. Most importantly, the stronger the behavioral adjustment to the switch trial likelihood was, the stronger the adjustment of anticipatory posterior alpha lateralization. We conclude that anticipatory spatial attention is reflected in the distribution of posterior alpha band power, which is predictive of individual detection performance in response to the implicit statistical properties of the task.

2.1 Introduction

When driving down a long and lonesome road, you can probably attend to the road while also talking to your passenger. As you head towards a crowded crossing, you will gradually focus your attention to the traffic and eventually stop talking to your passenger. After having passed the crossing you can allow yourself to again attend to your passenger.

This example illustrates our ability to gradually adjust our attentional resources according to the surrounding. This process is likely to be associated with a gradual engagement and disengagement of brain regions processing respectively relevant or irrelevant for the task at hand. We hypothesize that this redistribution of resources is partly reflected by a differential adjustment of neural oscillations in various brain regions. Recent findings suggest that oscillatory alpha activity (7-13Hz) plays a role in the distribution of attention resources by functional inhibition of sensory regions. This allows for filtering incoming information (reviewed in Bonnefond and Jensen, 2012; Foxe and Snyder, 2011; Jensen et al., 2012; Jensen and Mazaheri, 2010; Klimesch, 2012, 1999) . The main idea is that alpha activity increases in sensory regions associated with suppression of task-irrelevant information, while alpha activity decreases in regions processing the task-relevant information. For instance, recent studies on visual covert attention have demonstrated that alpha power decreases in the parieto-occipital regions contralateral to the anticipated stimuli whereas alpha activity increases relatively in ipsilateral parieto-occipital regions (Worden et al., 2000). In a visuo-spatial detection task, Thut et al. (2006) demonstrated that the degree of prestimulus hemispheric alpha lateralization correlated with faster target detections. Kelly et al. (2009) and Händel et al. (2011) showed that the strength of prestimulus alpha lateralization is predictive of target discriminability. These studies indicate that hemispheric alpha lateralization correlates with enhanced performance in spatial attention tasks. Finally, Romei et al. (2010) demonstrated that TMS can be applied to entrain alpha oscillations over the parietal cortex ipsi-lateral to the attended direction. Since this entrainment had positive consequences for performance in a spatial attention task, one can argue for a causal inhibitory role of the alpha oscillations.

Two recent studies provided strong evidence for alpha power being under top-down control by demonstrating that prestimulus hemispheric alpha lateralization is influenced by explicit manipulation of the reliability of the spatial cue (i.e. a cue indicating the visual hemifield to covertly attend to). Haegens and colleagues (2011a) conducted a spatial somatosensory dis-

crimination task in which subjects were explicitly informed about the cue reliability. They found that the reliability of the cue correlated with the prestimulus alpha power lateralization in sensorimotor regions. A related study was performed by Gould and colleagues (2011) in the visual domain. They found a linear increase in alpha lateralization in visual regions with cue reliability. Furthermore, subjects with a stronger alpha power decrease contralateral to the cue also showed a stronger behavioral cueing effect as reflected in faster reaction times. These two studies show that alpha power in both visual and somatosensory regions is modulated by expectations about the likelihood of external events.

In these paradigms attention biasing was manipulated using explicit cues. In real life, however, attention biasing is often modulated by statistical properties of events in the environment. The aim of our current study was to assess whether biases in the allocation of attention due to statistical properties in the environment are reflected in anticipatory alpha-band lateralization. In a visual covert attention paradigm subjects were instructed to detect a stream of targets occurring in one hemifield. However, they had to switch attention to the unattended hemifield when a stimulus change occurred in the unattended side. The likelihood of an attention-switch-stimulus (indicating an attention switch trial) increased with the number of trials following the previous switch; however, the subjects were not explicitly informed about this statistical property. We assessed the individual change in alpha lateralization and switch-trial detection rate with switch-trial likelihood. Our study provides evidence that subjects who adapted their behavior (i.e. switch trial detection rate) according to the statistical properties of the task (switch-trial likelihood) also were the ones who adjusted their hemispheric alpha lateralization accordingly.

2.2 Materials and Methods

Participants

Twenty healthy subjects with normal or corrected-to-normal vision (mean age: 24 ± (SD) 4 years) participated in the experiment after providing written informed consent according to the Declaration of Helsinki and the local Ethics board. The subjects did not have neurological or psychiatric disorders. The study was approved by the local ethics committee (CMO region Arnhem / Nijmegen).

Stimulus presentation and experimental paradigm

Stimulus presentation was performed using Presentation (Neurobehavioural Systems, Inc.) and a liquid crystal display video projector (SANYO PROxtraX multiverse; refresh rate of 60 Hz), back projecting onto a screen in the magnetically shielded room using two front-silvered mirrors. The distance to the screen as well as the size of the displayed screen size were measured individually for each subject. This allowed us to compute stimulus sizes and distances in visual degrees ensuring the same stimulus properties across subjects.

We developed a covert attention switching paradigm based on the study of van Schouwenburg et al. (2010, see Figure 1). Squares were flashed on each side and subjects had to report the color of the attended square by a button press. When subjects detected a color change at the unattended side (signaling a *switch trial*), they had to report the color of the unattended square (but not the currently attended square) and switch attention to the unattended side in future trials.

At the beginning of each block, subjects were explicitly cued to which side to attend. From then on, the attended side was determined by stimuli properties alone. A central fixation point was presented during the entire experiment. Colored squares were flashed 1200ms after the beginning of each trial for about 33 ms (two frames=2/60Hz). These stimuli were presented with nine degrees eccentricity and two degrees lower than the fixation cross (measured from the fixation cross to the center of the stimuli). The squares were two degrees wide.

Subjects had to report the color of the square on the attended side by pressing a button with their left (for red) or right hand (for blue). On the unattended side, the square was either grey (*repeat trials*) or colored in blue or red (*switch trials*). Subjects had to respond within 2500 ms. After responding, the fixation cross turned grey, indicating that the subject could blink or move the eyes in a 1000 ms period. Then the fixation cross turned white again indicating the start of the next trial. Subjects had to keep attention to one hemifield (*repeat trial*) and report the color of the square on that side until they detected a colored stimulus in the unattended hemifield (switch stimulus). A trial which includes a switch stimulus is called a *switch trial*. The switch stimulus was detected if the color of the unattended target was correctly reported (*detected switch trial*). Subjects then had to keep attending the formerly unattended hemifield until a next switch trial was detected. If a subject failed to detect the switch stimulus (*undetected switch trial*), it was repeated with a random color (blue or red) up to four times.

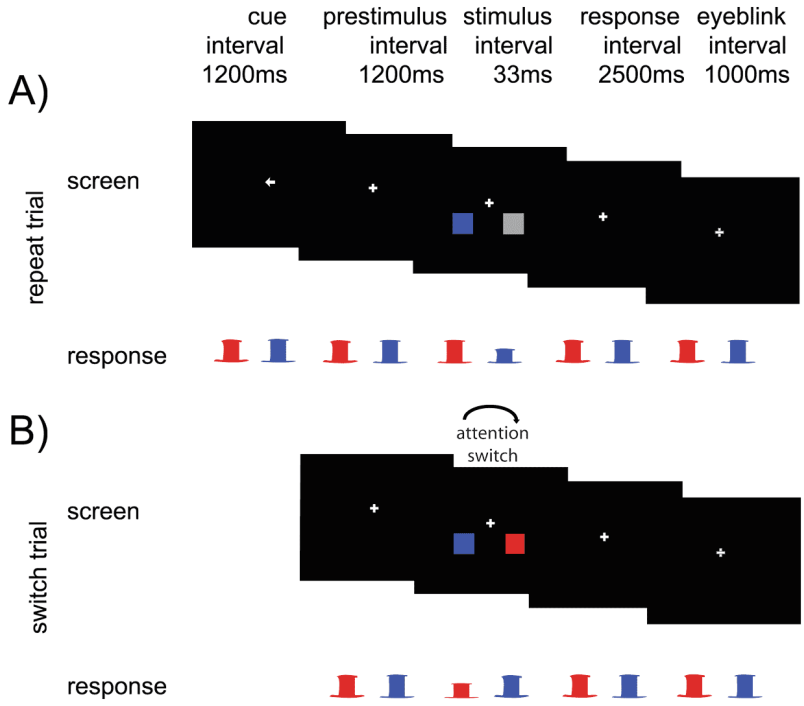


Figure 1 The paradigm. The attended side was initially indicated by a cue. Subjects had to focus at the fixation cross and by button press indicate the color of the attended squares (left button for red and right button for blue). The 1200 ms prestimulus period was followed by the colored stimuli flashed for 33 ms. Subjects had to respond within 2500 ms. If there was a color change in the square of the unattended hemifield, attention had to switch to that direction ('switch-trial). After the response there was a 1000 ms window for eye blinking. A Example of an explicit cue followed by a repeat trial. The subject had to covertly attend to the left and subsequently report the color of the stimuli by pressing the corresponding button (here: blue, right button). B Example of a switch trial. In the previous repeat trials, the subject had to attend to the left, because of the initially shown spatial cue. Upon stimulus presentation, the subject correctly switched attention and indicated so by reporting the color of the stimulus at the formerly unattended side (here: right, red color). If the subject responded according to the formerly attended side (here: left, blue), the switch trial would repeat up to four times. Repetitions of switch trials were removed from the analysis. If the subject did not switch after the fourth consecutive switch trial, another explicit spatial cue pointing to the formerly unattended side was presented (here: a rightward pointing arrow).

We focused the analysis on the first switch trials, i.e. dismissed switch trials immediately following an *undetected switch trial*.

The probability of a switch trial was increasing with the number of trials since the last switch trial (see Figure 2). The number of trials between switches was precomputed, so that the sequence of trials was as similar as possible across different subjects (on average 4.5 trials). We call the number of trials from the last switch trial *Inter-Switch Trial Number* (ISTN). A number of *detected repeat trials* were required to trigger a switch trial. When a subject made a wrong response to a repeat trial, the trial number from the last switch trial was reset. Thus a number of consecutive correct responses to repeat trials were needed to trigger a switch trial. This ensured that subjects did not only attend the supposedly unattended side throughout the experiment. The number of response errors to repeat trials was, however, very low (<10%, see also **Chapter 3.1** *Behavioral Results*). Our setup resulted in a linear increase in switch trial likelihood with ISTN (see Figure 2). Subjects were given a break of at least 2.5 seconds after every 15th *detected switch trial*. After each break, an explicit spatial cue indicated the initially attended side. Additional explicit spatial cues were provided after four *undetected switch trials* and after four errors to repeat trials in between two switch trials (5.2 ± (SD) 3.9 cues for attention to the left and 5.9 ± (SD) 4.4 cues for attention to the right). The experiment was terminated after the first *detected switch trial* 60 minutes after the experiment began.

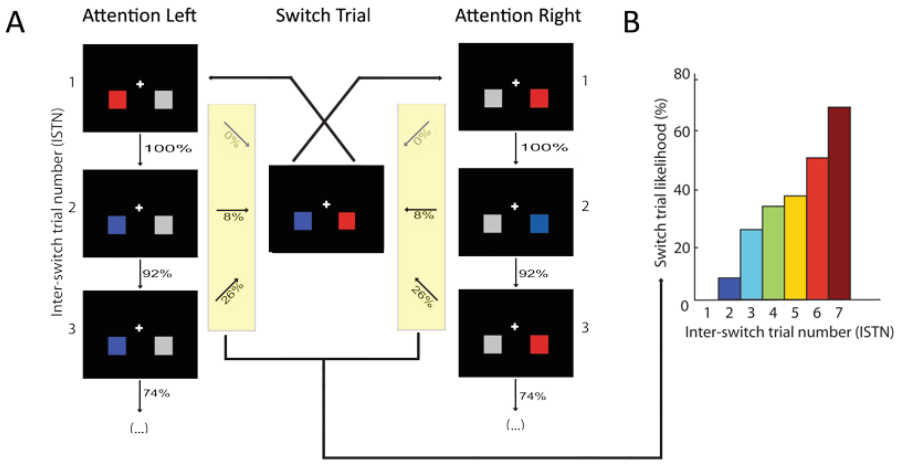


Figure 2 Relation between switch-trial occurrence and Inter-switch trial number (ISTN). **A** The likelihood that a switch trial would occur (i.e. the hazard rate) was independent of the attended side, but increased as function of trials since the last switch trial. More repeat trials since the last switch trial made it more likely that the next trial could be a switch trial. **B** The likelihood of switch trial occurrences (i.e. the hazard rate) linearly increased with ISTN.

In order to make the task sufficiently difficult, the intensity of the stimuli was varied across subjects and trials in an adaptive staircase-like procedure on a 20-step scale (1:darkest; 20:brightest), starting at 10 for both the neutral and the colored stimuli. This was done in the first block (i.e. until the 15th *detected* switch trial). The intensities of the neutral and colored stimuli were modulated according to different criteria. Repeat trials should be sufficiently demanding while keeping response errors as low as possible. Therefore we kept reducing the brightness of the colored stimuli to a level in which the subject could perform the discrimination with no errors. The color intensity was reduced by one step after each *detected switch trial* and if no errors to repeat trials were made before. After a response error to repeat trials, the intensity was increased by one step again. The intensity of the neutral stimulus was adapted to manipulate the difficulty of switch trials. A large intensity difference between colored and neutral stimuli makes detection of switch trials easier (pop-out effect), whereas a similar intensity results in a harder task and less detected switch trials. We aimed at a correct response rate to switch trials between 25% and 75%. After a detected switch trial, the neutral stimulus was increased in intensity by one when less than 25% of all switch trials were detected. The intensity was decreased by one step when more than 75% of all switch trials were detected. The twenty levels of stimulus luminance were visually and mathematically matched according to the CIELAB specifications (Rubner et al., 1998; Ruzon and Tomasi, 1999). This procedure resulted in similar intensities across most subjects. Subject 4, 7 and 18, however, were exposed to a brighter neutral stimulus (level 11, 9 and 9, respectively, versus level 2 or 3). Subject 4 and 7 were also exposed to brighter colored stimuli (contrast level 9 and 6 versus 1 to 4). These subjects showed no differences in behavioral performance compared to all other subjects and were thus included in further analysis. Note that the adaptation procedure was only done in the first block until the 15th detected switch trial. Trials from this block were not included in the analyses.

Prior to the experiment, participants received written and verbal task instructions. Subjects were instructed to prioritize accuracy rather than speed, but were informed that they had should respond within 2.5s. They were instructed to detect the color at the cued side, but switch attention to the uncued side if the color at that side turned from grey to either blue or red. Subjects were informed that they would receive no response feedback. The instructions did not inform about the task statistics. After the instructions, subjects had to complete a short tutorial on the computer, which explained the paradigm and introduced the stimuli. To diminish learning effects, subjects performed a short test run in a separate, acoustically

shielded room. The test run had exactly the same properties as the final experimental run and included 30 *detected switch trials* (approximately 10 minutes). Afterwards, participants were seated upright in the MEG system in a comfortable position. They were instructed to sit as still as possible while fixating centrally. In our analysis, as already reported above, we discarded all trials up to the first experimental break.

Data acquisition

The ongoing brain activity was recorded using a whole-head MEG system with 275 axial gradiometers (CTF MEG Systems, VSM MedTech Ltd.) at a sampling frequency of 1200 Hz. After acquisition, data were resampled at 600 Hz. During the experiment, the subject's head position was continuously recorded using three coils, one placed at each ear canal (mounted on earplugs) and one at the nasion (Stolk et al., 2013). When the subject's head moved such that any coil was more than 2.5 mm away from its initial position, the head was realigned during the next break. In addition, an EyeLink 1000 eyetracker (http://www.sr-research.com) was used to track potential saccades.

Additionally, we acquired individual, high-resolution anatomical images using a 1.5T Siemens Magnetom Sonata system (Erlangen, Germany) with 1mm isotropic voxel size. To co-register the MEG and anatomical MR data, we used the same earplugs as in the MEG measurement with additional vitamin E capsules during the anatomical scan.

Data analysis

We computed the response rate to repeat trials (*number of detected repeat trials* divided by *total amount of repeat trials*), the switch-rate (*number of detected switch trials* divided by *total amount of switch trials*) and the mean reaction time (*RT*) to repeat and switch trials. Further, we separated trials into seven bins according to the number of trials from the last switch trial (i.e. according to the inter-switch trial number, ISTN). Trials after the seventh ISTN bin were dismissed from further analysis since the number of trials was too little for further analysis (less than 16 trials). Also, we dismissed switch trials that immediately succeeded an *undetected switch trial*, i.e. we only analyzed *switch trials* that were preceded by at least one *repeat trial*. Note that the switch trial likelihood for the first ISTN bin is zero, thus there are no measures of switch trials in ISTN bin 1. All results are reported in the format of sample mean ± standard deviation.

The MEG data were analyzed using the Matlab-based FieldTrip toolbox, developed at the Donders Institute for Brain, Cognition and Behaviour

(Oostenveld et al., 2011). Artifacts were detected in a semi-automatic fashion, which included visual inspection and trial rejection based on variance and other measures as implemented in FieldTrip. We focused artifact rejection in the window from -1 s to 0.5 s relative to stimulus onset. We excluded trials in which the head position exceeded 5 mm from the average position throughout the experiment. Based on the eye-tracker data, we excluded trials with eye saccades exceeding 3 visual degrees from the fixation cross or eye blinks. On average around 29% of the trials were excluded, mainly because of eye blinks or movements. For the sensor-level analysis, the combined planar gradients of the MEG field distribution were estimated using a nearest neighbor procedure, similar to the method described by (Bastiaansen and Knösche, 2000).

Spectral analysis

We computed the time-frequency representations (TFRs) of power from 2 to 32 Hz (1 Hz increments) for each trial from a -1.0 s to 0.5 s interval around the stimulus onset. Spectral content was estimated using an adaptive sliding window of four cycles per frequency bin (e.g. Δt=400 ms for 10 Hz), which was multiplied with a Hanning window prior to applying a fast Fourier transform. For further analyses, we computed the non-time resolved power spectrum from -1 s to 0s using a Hanning-tapered Fast Fourier Transform. This time-period was chosen because our main hypothesis pertained to anticipatory processes. From these power spectra we extracted power in the individual alpha-band (see below) at the sensors of interest.

Alpha modulation index computation

We will refer to the alpha modulation as the difference of power in the alpha-band between trials in the condition attention left and attention right in the prestimulus interval. For each subject we calculated the alpha modulation index (AMI) defined as follows:

$$AMI_L := \log\left(\frac{\vec{\alpha}_L}{\overleftarrow{\alpha}_L}\right) \;\; ; \;\; AMI_R := \log\left(\frac{\vec{\alpha}_R}{\overleftarrow{\alpha}_R}\right)$$

$$AMI := AMI_L - AMI_R = \log\left(\frac{\vec{\alpha}_L}{\overleftarrow{\alpha}_L}\right) - \log\left(\frac{\vec{\alpha}_R}{\overleftarrow{\alpha}_R}\right) = \log\left(\frac{\vec{\alpha}_L \vec{\alpha}_R}{\overleftarrow{\alpha}_L \overleftarrow{\alpha}_R}\right) = \log\left(\frac{\vec{\alpha}_L}{\overleftarrow{\alpha}_R}\right) - \log\left(\frac{\vec{\alpha}_L}{\overleftarrow{\alpha}_R}\right)$$

Here, α denotes power in the alpha-band. The subscripts L and R denote the sensors of interest over the left and right hemisphere, respectively. The arrow above α denotes the condition, namely attention left and attention

right. Thus, $\vec{\alpha}_L$ and $\vec{\alpha}_R$ denote alpha-band power in the sensors of interest over the left and right hemisphere, respectively, in the average of all attention right trials. $\overleftarrow{\alpha}_L$ and $\overleftarrow{\alpha}_R$ denote the equivalent with respective attention to the left hemifield. These AMI measures reflect the modulation of alpha band activity with respect to spatial attention to the left and the right. When comparing attention to the left versus the right, AMI_L will be positive, and the AMI_R will be negative. This corresponds to a relative ipsilateral increase and contralateral decrease in alpha power. Thus, a positive AMI reflects the degree of hemispheric lateralization and thus attention toward the attended side (cf. Gould et al., 2011; Haegens et al., 2011a; Thut et al., 2006). A negative AMI reflects a high degree of attention to the side where the switch stimulus will appear. The attended side changed after each *detected switch trial*.

In order to optimize sensitivity of the analysis, we focused the analysis on the band around the individual alpha frequency (IAF; Klimesch, 1999) to which we will refer to as the individual alpha-band (Thut et al., 2006). The IAF is determined by the peak frequency in the 7-13 Hz spectrum. The individual alpha-band is defined from 4Hz below to 2Hz above the IAF. The average peak frequency across subjects was 10.5Hz±(SD)0.64Hz, which is ~1.5Hz lower than what Worden et al. (2000) and Thut et al (2006) reported , but close to the findings of Sauseng et al (2005).

To define the sensors of interest for pre-stimulus analyses, we computed the relative difference in alpha-band power induced by the stimulus (0 to 0.5 seconds, see Figure 4A) between attention left and attention right trials for all *repeat trials*. We selected twelve sensors with the strongest positive induced response and twelve sensors with the strongest negative induced response for the left versus right attention contrast. These sensors will be referred to as the left and right regions of interest (ROI), which were subsequently used to compute the AMI_L, AMI_R and AMI per ISTN.

To assess individual differences in performance, we performed a linear trend analysis on the above mentioned binning scheme (ISTN), expecting a linear relationship between the ISTN, AMI and behavioral measures. We restricted the analysis to a linear trend, because a linear relationship between explicit instruction cues and behavioral and neural measures was found by Gould et al., (2011) and Haegens et al., (2011a). Moreover, we also computed a within-subject linear regression between these measures.

Source analysis

We used a beamforming approach based on an adaptive spatial filtering technique (Dynamic Imaging of Coherent Sources, DICS) to localize the underlying sources of the alpha band activity (Gross et al., 2001; Schoffelen et al., 2008). The subject specific anatomical brain scans were discretized with a resolution of 1cm. We used a realistically shaped single shell head model based on the subject specific anatomical MRI to compute the lead-field per grid point (Nolte, 2003). The beamforming algorithm computes a spatial filter per grid point using the cross-spectral density matrix obtained from a Fourier transform. We computed the cross-spectral density matrix based on the interval from -1s to 0s relative to stimulus onset. The Fourier spectrum was centered on 10 Hz computed using five Slepian tapers (Percival and Walden, 1993), i.e. a 3 Hz smoothing, resulting in an estimate of 7-13 Hz. To allow averaging over subjects, we normalized subject individual head models by inversely warping it to the MNI template brain (International Consortium for Brain Mapping, Montreal Neurological Institute, Canada) using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). Based on all trials a spatial filter was computed, which we used to estimate source activity of attention left and attention right trials separately.

Statistical analysis

Statistical analysis of behavioral data was performed using a repeated measured analysis of variance (ANOVA) using the factors trial type (repeat or switch trial) and attended hemifield (left or right). For analysis of reaction times, we additionally included the correct response rate as a factor. Further behavioral analyses were conducted using paired t-test.

Statistical significance of neural data was assessed using a non-parametric cluster-based permutation test (Maris and Oostenveld, 2007). In the cluster-based permutation test, notational significant clusters in channel/grid space are detected using a parametric test-statistic, here the t-statistic thresholded by an uncorrected p-value (0.05 for sensor level data and 0.025 for source level analysis to get spatially more defined cluster). Then values in channel/grid tiles are reshuffled randomly between the conditions and the maximum cluster size per permutation is stored to assess the distribution of maximal cluster sizes. Cluster size is defined as the sum of the t-values in that cluster. Cluster significance in the original contrast is assessed by comparing their cluster size with the distribution of the maximal cluster sizes across permutations. A cluster-based permutation test therefore controls for multiple comparisons. We considered a cluster to be significant at alpha=0.05 (two-sided), thus if the cluster size lies above or below 2.5% of the permutation distribution. To determine the regions of

interest, we averaged over time and frequency of interest (here -1s to 0s, and 7Hz to 13Hz) to yield clusters in channel/grid space. 2000 permutations were used to estimate the distribution of maximal cluster sizes on sensor level; 5000 permutations were used for the source level data.

2.3 Results

Behavioral performance

The subjects were asked to perform the task described in Figure 1. We recorded 1018±98 (mean ± standard deviation) trials per subject and 722±122 trials were left after artifact rejection; 151±21 of them were *switch trials*, i.e. trials which include a switch stimulus (see **Chapter 2.2** *Stimulus presentation and experimental paradigm*). We expected the detection of switch trials to be more difficult than the detection of repeat trials, i.e. to be associated with longer reaction times and more errors (van Schouwenburg, 2010). Figure 3A and D provide an overview of the behavioral data for respectively response rates and reaction times. A 2-by-2 ANOVA on response rates with the factors attended hemifield (left or right) and trial type (repeat or switch trial) revealed a main effect of trial type ($F(1, 77)=72.88$, $p<0.01$). On average, subjects responded correctly to 91.2±4.6% of all repeat trials and detected 64.2±18.7% of all switch trials (*switch-rate*) resulting in 105±20 detected switch trials. We did not find a significant effect of hemifield ($F(1, 77)=0.01$, $p>0.9$) or a significant interaction between the two factors ($F(1,77)=0.14$, $p>0.7$).

Table 1: Number of trials after artifact rejection per ISTN bin.

ISTN bin	Total #trials	Trials, attention left	Trials,attention right
1	111.5 ± 17.9	55.3 ± 9.5	56.3 ± 9.1
2	112.8 ± 17.8	55.4 ± 8.6	57.5 ± 10.0
3	109.3 ± 18.7	54.7 ± 9.6	54.6 ± 10.2
4	96.5 ± 18.6	47.6 ± 9.4	48.9 ± 10.0
5	73.0 ± 14.1	35.8 ± 7.6	37.2 ± 7.5
6	51.4 ± 14.1	23.9 ± 6.7	27.5 ± 6.0
7	36.3 ± 11.3	17.2 ± 4.4	19.1 ± 5.0

To quantify the reaction time effects, we conducted a 2-by-2-by-2 ANOVA with the factors attended hemifield (left or right), trial type (repeat or switch trial) and correctness of response. A significant main effect of trial type ($F(1, 153)=14.93$, $p<0.01$) revealed that subjects responded significantly

slower to switch trials (995±234ms) than to repeat trials (787±148ms). There was no main effect of hemifield ($F(1, 153)=0.68$, $p>0.4$). Furthermore, there was a significant interaction between trial type and correctness of response ($F(1, 153)=27.35$, $p<0.01$). Using a post-hoc t-test we found that reaction times to detected switch trials were significantly longer than to undetected switch trials (difference: 131±165ms, $t(19)=3.55$, $p<0.01$, *uncorrected*), while reaction times to repeat trials were significantly slower for correct responses than for errors (-251±147ms, $t(19)=2.73$, $p<0.05$, *uncorrected*).We conclude that responses to switch trials required more effort than to repeat trials, independently of the attended hemifield, as reflected in increased reaction times and reduced response rates.

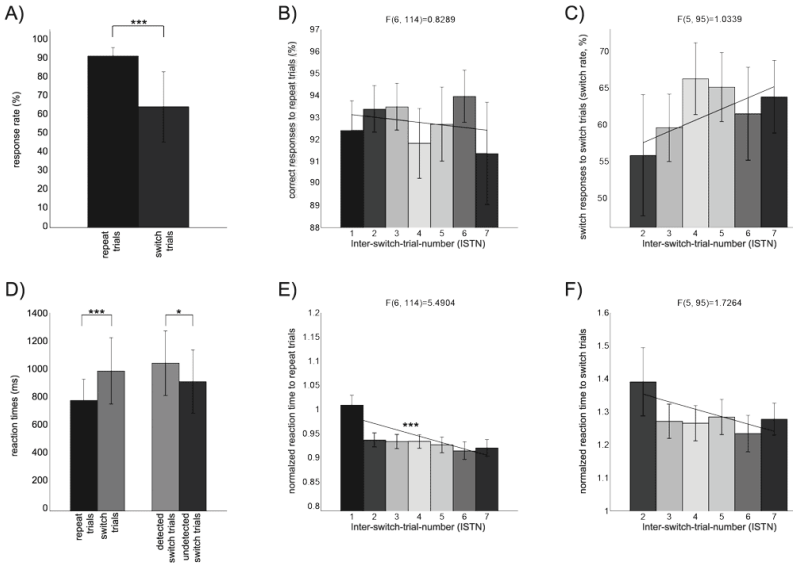


Figure 3 Behavioral results. A Mean rate of correct responses to repeat and switch trials averaged over all subjects and ISTN bins. The correct response rate was lower for switch trials than for repeat trials ($F(1, 77)=72.88$, $p<0.01$) B There was no significant linear trend over ISTN bins in terms of correct responses to repeat trials ($F(6, 114) =0.8289$, $p=0.55$). C There was no significant linear trend over ISTN bins with switch-rate ($F(5, 95)=1.0339$, $p=0.40$). Note that the paradigm was designed so that there were no switch trials in ISTN bin 1; therefore the linear trend analysis starts at ISTN bin 2. D Reaction times to repeat trials were significantly lower than to switch trials ($F(1, 153)=14.93$, $p<0.01$). A post-hoc t-test indicated that responses to detected switch trials were faster than to undetected switch trials ($t(19)=2.73$, $p<0.05$, *uncorrected*) E There was a significant negative linear trend for reaction time to repeat trials over ISTN bins ($F(6, 114)=5.54904$, $p<0.01$). A trend analysis without the first ISTN bin showed no significant trend anymore ($F(5, 95) = 0.6585$, $p=.66$). F There was no significant linear trend between reaction times to switch trials and ISTN bins ($F(5, 95(=1.7264$, $p=0.14$). Horizontal lines depict the within-subject regression line. For illustration purposes, reaction times were normalized by the average reaction time of all trials per subject before averaging across subjects. *** indicates a significant effect with $p<0.01$, * indicates a significant effect with $p<0.05$

Subjects showed a linear decrease in reaction time for repeat trials ($F(6, 114)=5.4904$, $p<0.01$) with ISTN, but this was entirely driven by the first ISTN bin following attention switches. A trend analysis without the first ISTN bin showed no significant trend anymore ($F(5, 95) = 0.6585$, $p=.66$). We interpret as an attention switch cost effect (see e.g. Monsell, 2003) after subjects reallocated spatial attention and therefore adjusted to task changes. Because of the observed attention switch cost and because ISTN bin 1 has no switch trials, we conducted all subsequent analyses from ISTN bin 2 onwards. For switch trials, we hypothesized that the subjects' performance would be relatively low for early and thus unexpected switch trials and but gradually improve for later switch trials. In the grand average, we did not, however, find a linear trend between ISTN bin and detection rate of switch trials ($F(5, 95)=1.0339$, $p=0.40$). There were no other significant effects in the grand average. Thus, in the data averaged over subject, we did not find proof of behavioral adjustments to the task statistics.

Prestimulus alpha modulation

We next considered the neuronal mechanism of anticipatory attention as characterized by hemispheric specific alpha band modulations. In our main analysis, we focused on the alpha-modulation index (AMI) by contrasting the alpha power between contra- and ipsilateral attention for each hemisphere separately and in combination (see **Chapter 2.2** *Alpha modulation index computation*).

Figure 4A and 4B show the topographic distribution of the alpha band modulation, i.e. alpha-band power (7-13Hz) per sensor when contrasting attention left and attention right trials. To determine the sensors of interest for later analysis on the pre-stimulus interval, we selected sensors with the strongest induced response to the stimuli in repeat trials in the alpha band. The twelve left sensors showing the strongest positive stimulus induced alpha modulation and the twelve right sensors showing the strongest negative induced alpha modulation (Figure 4A, marked with asterisks) were selected for further analysis to compute the alpha modulation index (AMI). We will refer to these as regions of interest (ROI). The remaining analyses were performed in the prestimulus interval (depicted in Figure 4B, 4C and 4D). We performed a source-reconstruction analysis in the prestimulus interval (-1s to 0s) and in the alpha-band (7-13 Hz). The analysis on source-level confirmed a significant left parieto-occipital power increase (Figure 4C; cluster-based permutation test, $p<0.05$).

To verify whether the alpha band activity was modulated by attention in the prestimulus window, we performed a cluster-based permutation test

over all sensors. We found one significant cluster over left parieto-occipital regions in the contrast attention left versus attention right (p=0.02). This cluster included eight of the twelve pre-selected left ROI channels, confirming the appropriateness of the selected ROI. In the right hemisphere sensors we did not find evidence for significant anticipatory alpha band modulation with attention. Figure 4D shows the time-frequency representation of the left and right ROIs for the contrast attention left versus attention. In line with the cluster-based permutation statistics, alpha power appears higher in the left ROI for attention left compared to attention right. As expected the time-frequency decomposition shows induced, lateralized activity around 10Hz at ~200 ms after stimulus onset.

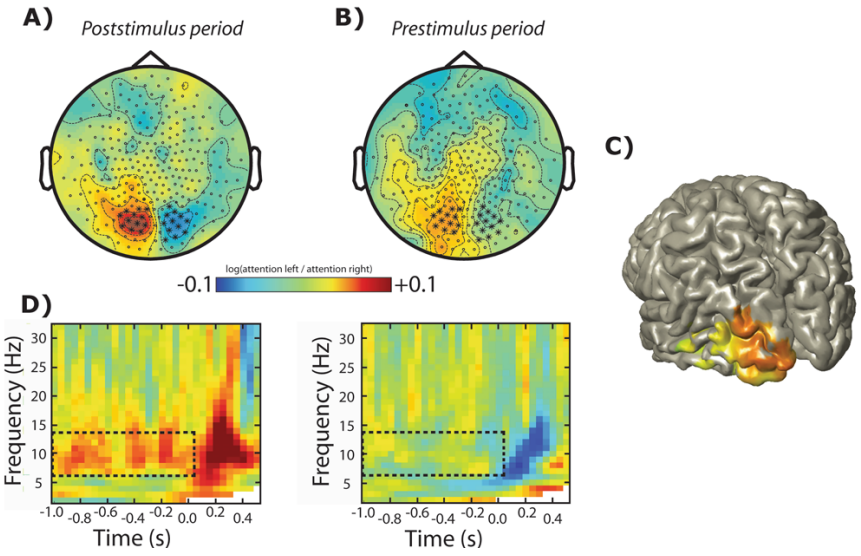


Figure 4 Alpha modulation and ROI selection. All plots show the contrast of attention left versus right repeat trials; grand-average. A Topographic map of stimulus-induced alpha-band (7-13Hz) modulation for all repeat trials (t=0 to 0.5s). The twelve most sensitive sensors on the left and on the right hemisphere in the induced alpha-band response were selected for further analysis (marked with asterisks). B Topographic map of prestimulus alpha-band modulation for all repeat trials (t=-1 to 0s). C Source reconstruction of the prestimulus alpha (7-13Hz) modulation (t=-1s to 0s). Only the significant cluster from the permutation test is depicted (p<0.05). D Time-frequency representation of power of the alpha modulation for the left and the right ROIs, respectively. The box (dotted lines) shows the frequency range chosen for Figure 4A, 4B and 4C and the chosen prestimulus interval for all further analyses as well as for Figure 4B and 4C

Next, we asked whether the ability to detect switch trials correlated with the magnitude of alpha power over the left or right ROI. We tested whether there was a difference between detected and undetected switch trials when considering the left minus right attention condition (independent of ISTN

bin). We did not find significant differences neither for the pre- nor for the poststimulus period (cluster-based permutation test, all p>0.1).

Individual behavioral and neural adaptation to switch trial likelihood

The likelihood that the next trial would have a switch trial increased with ISTN, i.e. with the number of trials since the last switch trial (see Figure 2). We expected subjects to adapt to the implicit change in switch trials likelihood, which will be reflected in behavioral and neural adaptation. As already reported (see **Chapter 2.3** *Behavioral results*), we did not find a systematic increase in detection rate with increasing ISTN on grand average level. Next, we computed the power spectra for the trials in each ISTN bin in the prestimulus interval and subsequently computed the AMI (the alpha modulation combined over the left and right ROI; see **Chapter 2.2** *Alpha modulation index computation*) per ISTN bin. In this analysis we neglected the first ISTN bin to reduce influences from attention switch costs (see **Chapter 2.3** *Behavioral results*). As for the behavioral analysis, we performed a linear trend analysis between the AMI as a function of ISTN bin, but found no significant effects in the grand average ($F(6, 114)=0.2830$, $p=0.94$). In the grandaverage alpha-modulation topography (Figure 4B) we found mainly left hemispheric modulation; however the left hemisphere AMI (AMI_L) did not systematically change with ISTN either ($F(6, 114)=0.955$, $p=0.46$). We additionally tested whether resetting the ISTN (see **Chapter 2.2** *Data analysis*) after an incorrect response to a repeat trial might have caused the lack of significant effects in the grand average. The ISTN resets could potentially have introduced variability into subjective probabilities. To do so, we again conducted the linear trend analysis of the alpha modulation index with ISTN bins, but removed blocks of trials with errors to repeat trials. The trend remained non-significant ($F(6, 114)=0.4973$, $p=0.81$). Importantly, we observed that the ability to detect the implicit likelihood of events strongly differed across participants. We computed the switch-rate for each ISTN bin and all subjects. Then, we correlated the switch-rate per ISTN bin with the switch-trial likelihood per ISTN bin (see Figure 2) for each subject. Next, we built the 95%-confidence interval (CI) around the mean of all correlation coefficients and investigated how many correlation coefficients were outside this interval. The confidence interval ranged from -0.09 to 0.45. We found eight subjects with a correlation coefficient below the lower bound of the CI and ten subjects with a correlation coefficient above the upper bound of the CI. Due to the wide spread of correlation coefficients, we concluded that there were large inter-individual differences in behaviorally adjusting to the parameters of the task.

Next, we asked whether the behavioral adjustment can be explained by an adjustment of posterior alpha modulation. To quantify this, we computed for each subject the regression slopes of the behavioral performance and of the AMI with respect to ISTN bins. We hypothesized that subjects with a more pronounced behavioral task adjustment (i.e. a better ability to detect switch trials) also adapted their alpha activity to the properties of the task. In other words, we expected a significant negative inter-subject correlation of these two regression slopes (better task performance should result in more attention to the unattended hemifield, thus a weaker AMI). The regression slope-slope correlation analysis revealed that an adaptation of the AMI to the task statistics does have these behavioral effects. Figure 5A shows the slope of switch-rate (y-axis) as a function of the slope of the alpha modulation index (x-axis) revealing a significant negative correlation (r^2=0.3096, p=0.01). The change in switch-rate is not explained by individual differences in speed-accuracy trade-off because there was no significant correlation between slope of AMI and reaction time for switch trials (r^2=0.0190, p>0.5, Figure 5B). For repeat trials, we did not find significant correlations, neither for the slope of the correct response rate (r^2=0.0909, p>0.1) nor for the slope of reaction times (r^2=0.0056, p>0.7). Also the number of ISTN resets per subject was not correlated with the switch rate slope (r^2= 0.0803, p=0.2260) or with the AMI slope (r^2=0.1429, p=0.10). The result remained significant when we included the AMI data from the first ISTN bin (switch-rate: r^2=0.2098, p=0.04), while reaction times to switch trials stayed not significant (switch trials RT: r^2=0.0082, p=0.70). Also for repeat trials, results stayed not significant when including the first ISTN bin (correct response rate to repeat trials: r^2=0.0264, p=0.49; repeat trial RT: r^2=0.0255, p=0.50). In short, this analysis demonstrates that subjects that adapted their alpha modulation according to the task statistics also detected more switch trials with increasing ISTN. Likewise, subjects that did not adapt the alpha modulation got worse at detecting the switch trials with increasing ISTN.

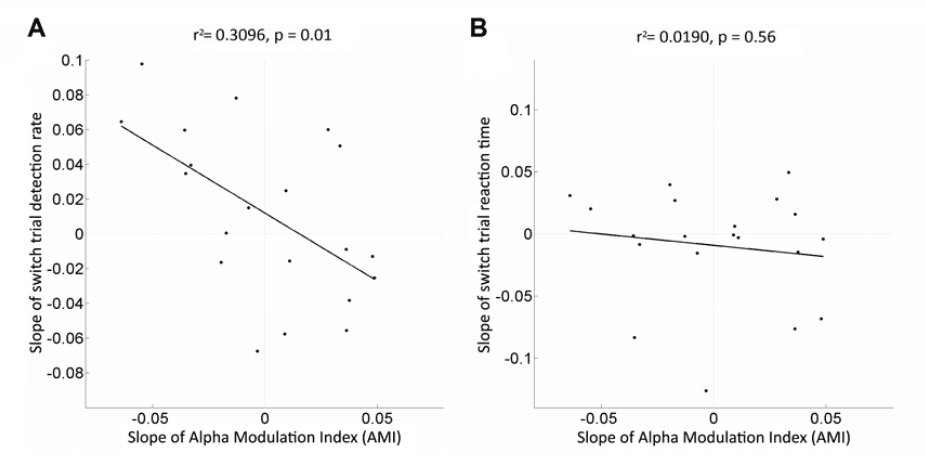


Figure 5 Regression slope-slope correlations across subjects when relating the AMI to behavioral measures. A Correlation of AMI slopes and switch-rate slopes. The slopes of switch-rate correlated strongly with the slopes of the AMI (r^2=0.3096, p=0.01). A subject with a negative AMI slope and a positive switch-rate slope suggests that this subject adjusts to the implicit change in switch trial likelihood. A subject with the opposite pattern (positive AMI slope and a negative switch-rate slope) suggests that this subject did not adjust properly to the implicit change in switch trial likelihood. Thus, subjects that adapted their AMI to the task statistics were also those who got better in switching with increasing ISTN. B Correlation of AMI slopes and switch-trial reaction time slopes. There was no significant correlation between AMI slopes and slopes of switch trial reaction time (r^2=0.0190, p>0.56).

2.4 Discussion

In a covert attention switching paradigm, we have investigated how subjects adapt to statistical properties of the environment; here a linear increase in the likelihood of stimuli prompting a switch in spatial attention. We found individual differences in how subjects adjusted behaviorally to the increase in switch trial likelihood. Interestingly, the individual degree of adjustment of posterior alpha band lateralization to switch trials likelihood predicted how well subjects adjusted their behavior. We conclude that anticipatory alpha band lateralization reflects the allocation of spatial attention as modulated by the implicit statistical properties of the environment.

The posterior alpha rhythm reflects the state of anticipatory visual attention

Recent studies have shown that alpha power is modulated in anticipation of upcoming stimulus (e.g. Bonnefond and Jensen, 2012; Rohenkohl and Nobre, 2011; Thut et al., 2006; van Ede et al., 2012; Worden et al., 2000). Two recent studies suggest that this anticipatory alpha rhythm is modulated according to properties of the environment in both the visual and the somatosensory system (Gould et al., 2011; Haegens et al., 2011a). In both studies, there was significantly stronger hemispheric alpha lateralization for highly reliable as compared to unreliable cues. Complementary to these earlier reports, we show that top-down modulation of posterior alpha power does not require explicit knowledge about stimulation likelihood. Instead, the brain adapts implicitly to statistical properties of the environment which then is reflected in the spatial distribution of alpha power preceding the stimulus. Crucially, we found that the strength of pre-stimulus alpha power predicted the magnitude of behavioral adjustment in individual subjects. This demonstrates that subjects who manage to adjust alpha power lateralization appropriately to the statistics of the environment are able to optimize their individual behavioral performance.

In the grand average of the prestimulus interval, we found a significant modulation over the left hemisphere but not over the right hemisphere. In the somatosensory domain, a similar effect has been found for uninformative spatial cues during a covert attention task (Haegens et al., 2011a). In the visual domain, this difference between the left and right hemisphere is consistent with the classical visuospatial model of Heilman (Heilman and Van Den Abell, 1980) that posits that left parietal regions process right hemifield visual input, whereas right parietal regions process both hemifields (reviewed in Sack, 2009). As such the model predicts that the left hemisphere will be more strongly modulated than the right when spatial attention is changed between hemifields. This notion is directly supported by a TMS study that perturbed either the left or right inferior parietal sulci (IPS) and then characterized the prestimulus alpha-band activity in a covert attention task (Capotosto et al., 2012a). They found that interfering with the right IPS resulted in a bilateral increase in anticipatory alpha-band power over occipital cortex and consequent performance deficits, whereas stimulation of left IPS did not. Similarly, Sauseng and colleagues (2011) used TMS to perturb the left and right FEF and found that only disturbing the right FEF reduces fronto-parietal coupling in the alpha-band and impairs performance during visual spatial attention shifting. Thus, the right hemisphere might have a more global contribution during allocation of spatial

attention, which explains the lack of modulation over the right hemisphere when contrasting attention to the left versus right hemifield.

Behavioral performance, stimulus intensity and motivation

We found a significant correlation between posterior alpha power and performance in terms of attention switching. It is important to note that subjects were encouraged to prioritize accuracy over reaction times (RTs). This could explain why alpha power and reaction times did not correlate in contrast to previous reports (e.g. Gould et al., 2011; Kelly et al., 2009; Thut et al., 2006). We did however demonstrate a relation between performance and the ability to modulate prestimulus alpha power. In particular we found that the individual degree of alpha adjustment was correlated with performance changes. This difference could be explained by some subjects relying on detecting the stimulus driven appearance of switch trials rather than on the statistics of switch-stimuli likelihood. In our paradigm, stimulus intensities were individually adjusted for each subject (see **Chapter 2.2** *Stimulus presentation and experimental paradigm*). To test if differences in stimuli intensity explained the effects, we asked whether the relative difference in intensity between the neutral and the colored stimulus was correlated with the AMI slope or switch-rate slope over ISTN but this was not the case for the AMI slope (r^2=0.0703, p=0.26) nor for the switch-rate slope (r^2=0.0575, p=0.31). Another possible explanation might be that subjects who did not adjust the hemispheric alpha lateralization according to target likelihood did not understand the task or were less motivated. This would imply that non-adaptive subjects had worse performance. We therefore tested whether subjects with a positive AMI slope over ISTNs had a lower detection rate of repeat trials than subjects with a negative AMI slope; however, this was not the case (t(18)=-1.1212, p>0.2). A similar analysis considering the switch-rate also showed no significance (t(18)=-0.695, p>0.5). Thus while some subjects were better able at adapting to the implicit task design, this was not explained by differences in behavioral performance or by motivational factors.

Which networks might control the posterior alpha power?

We have shown that posterior alpha power is modulated in a top-down manner by incorporating implicit statistical knowledge about the environment. Direct top-down control on visual attention most likely stems from the frontal eye fields (FEF) via the intraparietal sulcus (IPS), which are part of the dorsal attention network (see Corbetta and Shulman, 2002; Kastner and Ungerleider, 2000). Capotosto and colleagues (2009) used transcranial magnetic stimulation (TMS) to perturb the FEF and IPS during the prepara-

tion interval in a covert attention paradigm. They found that this perturbation not only impaired detection performance, but also the task-modulated parieto-occipital alpha-band power. This study indicates that FEF and IPS are causally involved in the control of posterior alpha-band power.

Apart from neocortical connections, the FEF are also strongly connected to subcortical regions such as the superior colliculus (SC) (reviewed in Hikosaka et al., 2000; Munoz and Everling, 2004). Beside its involvement in saccade preparation and execution, the SC is sensitive to behaviorally important, salient events (see Boehnke and Munoz, 2008 for a review; Comoli et al., 2003) and is therefore likely to be engaged in subjects performing our paradigm. Furthermore, both the SC and the FEF are strongly connected to the basal ganglia (Hikosaka et al., 2000; Neggers et al., 2012). In a recent fMRI study, van Schouwenburg et al. (2010) found that the BOLD signal in the basal ganglia (BG) increased when a visual stimulus successfully produced a switch in visual attention. Thus, the BG is likely to be part of the network engaged in the current study. Van Schouwenburg et al. also found strong modulation of the inferior frontal gyrus (IFG) in response to salient stimulation changes. Further investigations are required to study the involvement of above mentioned regions and to establish the link between fronto-striatal networks and posterior networks. For such investigations, animal electrophysiology or fMRI recordings might be more sensitive than MEG recording due to their high spatial resolution.

Conclusion and Future Work

We found that anticipatory spatial attention is reflected in the distribution of posterior alpha band power which is predictive of individual detection performance in response to environmental task statistics. The hypothesis that alpha power reflects the anticipatory attention state of the subject could be applied in neurofeedback paradigms. Recently it has been shown that ADHD patients show a lack of sustaining a high degree of alpha lateralization (ter Huurne et al., 2013). A neurofeedback paradigm could aim at optimizing the subject's awareness of their state of attention by providing online feedback using a measure reflecting the posterior alpha power lateralization. This setup could be used in directly training the subjects' ability to modulate their alpha band activity.

Chapter 3

Modulation of posterior alpha activity by spatial attention allows for controlling a continuous brain-computer interface

This chapter is based on

Horschig, J.M., Oosterheert, W., Oostenveld, R., Jensen, O. (2014) Modulation of posterior alpha activity by spatial attention allows for controlling a continuous brain-computer interface. Brain Topography. doi:10.1007/s10548-014-0401-7

Abstract

Here we report that the modulation of alpha activity by covert attention can be used as a control signal in an online brain-computer interface, that it is reliable, and that it is robust. Subjects were instructed to orient covert visual attention to the left or right hemifield. We decoded the direction of attention from the magnetoencephalogram by a template matching classifier and provided the classification outcome to the subject in real-time using a novel graphical user interface. Training data for the templates were obtained from a Posner-cueing task conducted just before the BCI task. Eleven subjects participated in four sessions each. Eight of the subjects achieved classification rates significantly above chance level. Subjects were able to significantly increase their performance from the first to the second session. Individual patterns of posterior alpha power remained stable throughout the four sessions and did not change with increased performance. We conclude that posterior alpha power can successfully be used as a control signal in brain-computer interfaces. We also discuss several ideas for further improving the setup and propose future research based on solid hypothesis about behavioral consequences of modulating neuronal oscillations by brain computer interfacing.

3.1 Introduction

A functional brain-computer interface (BCI) to be used in natural settings must provide a robust and reliable output (van Gerven et al., 2009a). Most of the noninvasive BCI research focuses on using electrophysiological measurements due to their high temporal resolution. However, our daily environment is full of electromagnetic noise. Coping with environmental noise can be solved on two fronts: either by incorporating advanced signal analyses technique or by choosing a strong, robust control signal to start with. Alpha oscillations are the strongest measurable signals from the human brain by extracranial electrophysiology and they are strongly modulated by attention tasks (Klimesch, 2012). Therefore they constitute a putative robust control signal for communicating one's intention. Here, we provide evidence that posterior alpha-band activity can be used as a reliable control signal for continuous online brain-computer interfacing.

The role of human alpha oscillation in attention processes has been studied intensively in the past. Increased attention strongly involves the inhibition of task-irrelevant information. Recent investigations suggest that alpha-band activity reflects the degree of functional inhibition of sensory regions (Foxe and Snyder, 2011; Jensen et al., 2012; Jensen and Mazaheri, 2010; Klimesch, 2012, 1999). Sensory regions that are not involved in the current task are functionally disengaged and show high alpha activity. In contrast, low alpha activity can be observed in regions that are processing relevant information. During covert attention to either the left or right hemifield, the alpha lateralization thus reflects a relative suppression of the task-irrelevant ipsilateral hemisphere, resulting in increased alpha-band power. Likewise, the relative contralateral alpha-band decrease allows efficient processing in the task-relevant hemisphere processing the attended information.

In the past, hypothesis-driven brain-computer interfacing has been proposed as a tool to augment human behavior (Jensen et al., 2011, and see **Chapter 5**). This requires the control signal to satisfy three conditions: First, a brain-computer interface control signal should allow for fast and reliable classification (van Gerven et al., 2009a). Second, it must be a robust correlate of behavioral performance. In the past, the distribution of posterior alpha power has been successfully linked to behavioral performance (Händel et al., 2011; Kelly et al., 2009; Meeuwissen et al., 2011; Park et al., 2014; Thut et al., 2006). Third, in order to train human behavior, the control signal must be trainable as well. Here, we will corroborate findings that alpha oscillations provide a robust control signal independent of advanced

signal analyses techniques and we will show that training of alpha oscillations results in better classification by reduced trial-by-trial variability.

Several studies have used off-line analysis to show that alpha power is a robust signal which can be used in a BCI setup involving spatial attention. In 2005 Kelly et al. showed that posterior steady-state evoked response in the alpha-band power can potentially be used as a control signal for a brain-computer interface (Kelly et al., 2005). Their work was later extended by van Gerven and colleagues (2009a) who demonstrated that spontaneous alpha band activity modulated by spatial attention can be decoded as well. A similar approach was recently used by Tonin and colleagues (2012) showing that appropriate feature selection in time-frequency and sensor-space can improve classification performance. In 2007, Rihs and colleagues showed that the distribution of posterior alpha reflects two-dimensional attention mapping (Rihs et al., 2007), which can successfully be used for continuous two-dimensional control in an offline setting (Bahramisharif et al., 2010). Treder and colleagues (2011) further showed that visuo-spatial attention shifts can be decoded by using alpha-band power and that classification rates correlate with the strength of resting state alpha-power. While these studies do suggest that modulations in alpha power can be used for BCI control, all studies relied on offline analyses after data acquisition. Recently, Tonin and colleagues (2013) showed for the first time that covert attention brain-computer interfacing is possible using electroencephalography in an online setup.

Here we show that posterior alpha-band power can be used as a BCI control signal using magnetoencephalography (MEG). In contrast to the paradigm of Tonin et al. (2013), we present subjects with continuous feedback while performing the BCI task. In addition, we hypothesize that the strength of lateralized alpha power predicts the individual subjects' classification rate. Furthermore, we investigate whether the ability to gain control over the BCI signal increases over multiple sessions, specifically predicting that subjects will be able to improve their performance after the initial session. Lastly, we investigate the robustness of the alpha lateralization pattern, specifically predicting that is stable across sessions and tasks.

3.2 Materials and Methods

Participants

Eleven healthy subjects with normal or corrected-to-normal vision (mean age: 24.1 ± (SD) 4.2 years) participated in the experiment after providing written informed consent according to the Declaration of Helsinki and the

local Ethics board. All subjects were free of neurological or psychiatric disorder. The study was approved by the local ethics committee (CMO region Arnhem / Nijmegen).

Data acquisition

The ongoing brain activity was recorded using a whole-head magnetoencephalogram (MEG) system with 275 axial gradiometers (CTF MEG Systems, VSM MedTech Ltd.) at a sampling frequency of 1200 Hz. Our set-up consisted of four computers, see Figure 1. For online data streaming, we set up an IPC shared memory segment and network accessible buffer at the data "acquisition computer" using the FieldTrip MATLAB toolbox (Jensen et al., 2011; Oostenveld et al., 2011). Data from the buffer was read over a TCP network connection by the "realtime computer" that was dedicated to online signal analysis. The results of the online analysis were written back to the network buffer and read out by the "stimulus computer" that was dedicated to stimulus presentation and to experiment management. Finally, we used an EyeLink 1000 eyetracker (SR Research Ltd., Canada) with a dedicated "eye tracker computer" sending eye position and blink data to the acquisition computer.

During the experiment, the subject's head position was continuously recorded using three coils, two placed at the ear canals and one at the nasion. During inter-trial intervals and experimental breaks, when no other data processing occurred, the realtime computer analyzed the MEG data from the high frequency signals produced by the head coils and gave visual feedback about the current head position to the experimenter (Stolk et al., 2013). When any coil moved more than 2.5 mm away from its initial position, we instructed the subject during the next experimental break to realign his/her head to the initial head position and provided visual feedback of the head position to the subject (Stolk et al., 2013). In the beginning of the second, third and fourth session we realigned subjects to the head position of the first session. On average the head position varied by 8 +/- 3.8 mm across sessions.

The eye position and blinks were monitored using the eye tracker. Subjects were instructed to fixate on the center of the screen throughout the experiment. We provided feedback to the subject in case of eye blinks or when the eye position deviated more than three visual degrees from central fixation. Visual feedback was given by changing the color of the central fixation marker. In case of such artifacts, the training task was restarted in order to get an artifact-free signal. In the BCI task we provided the same visual feedback, but instead of restarting a trial we stopped upcoming classifications until a full artifact-free period was available again (for timing details, see below).

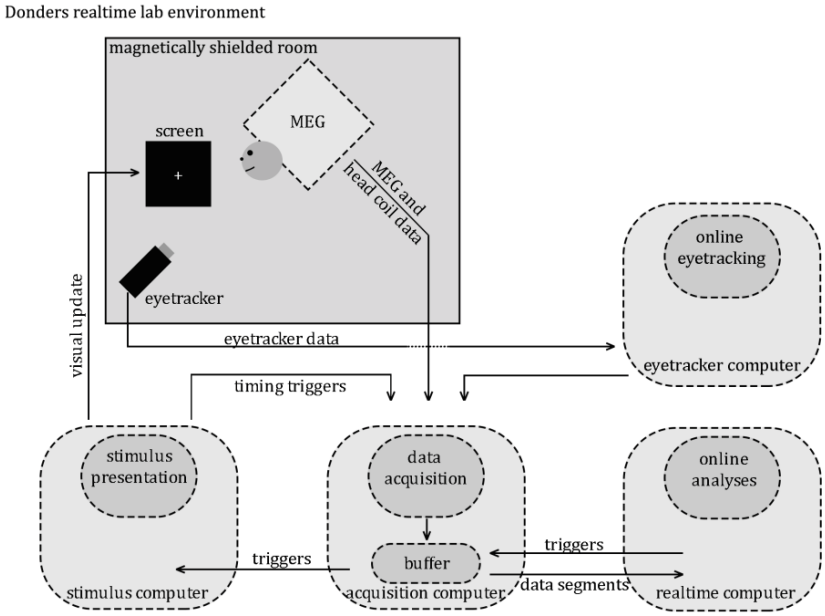


Figure 1 The BCI setup. The subject is seated in the magnetically shielded room. Data from the MEG system and eyetracker were sent to the "acquisition computer". The acquisition computer makes all data available in a shared memory segment from where it is copied to a network accessible buffer. The "realtime computer" polls the buffer continuously for relevant trigger values. Upon relevant triggers, i.e. during trials, the realtime computer reads data from the buffer, analyzes those and accordingly writes a trigger as control signal back to the buffer. The "stimulus computer" controls the experimental paradigm and provides visual output to the subject's screen. Visual output is either determined by the paradigm in the training task, or dependent on eye movements or on the classification outcome, in which case the stimulus computer reads the triggers from the buffer. Furthermore, the stimulus computer sends triggers indicating start and end time of individual trials to the buffer.

Experimental paradigm and stimulus presentation

OVERALL PROCEDURE Each subject participated in four sessions on separate days. Sessions were typically scheduled to be a maximum of one week (7 days) apart (on average 5 days +/- (SD) 5 days). Exceptions are Subjects 1, 2 and 6. Subject 1 had his second session nine days after the first session, and his last session 26 days after the third. Subject 2 had her second session 13 days after her first, and her last one 9 days after the third session. Subject 6 had his second session 13 days after his first. The overall procedure is depicted in Figure 2.

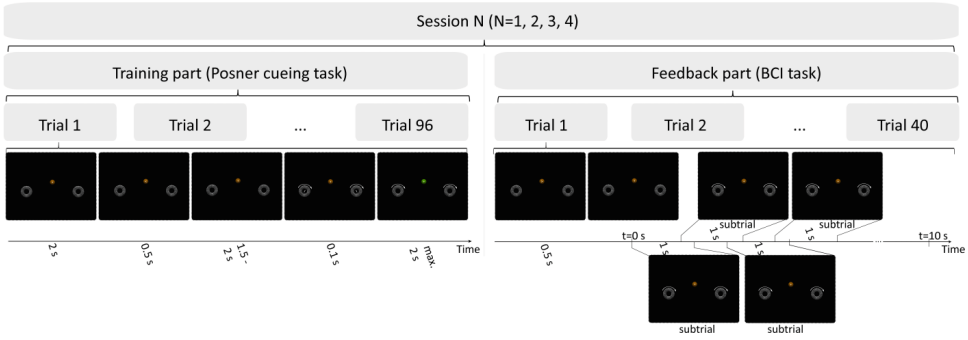


Figure 2 Experimental setup. Each subject participated in four sessions. Each session was split into a training part and a feedback part. The training part was a Posner-cueing task, which consisted of 96 trials, 48 for attention to the right and 48 for attention to the left. The feedback part, the online BCI task, consisted of 40 trials, each lasting 10 seconds.

Each session consisted of two tasks: a training task and a BCI task. The training part was used to determine individual templates of brain activity during covert spatial attention. In the BCI task these templates were used to decode the attended hemifield. The general stimulus setup for the training and BCI task were kept as similar as possible. Figure 3 shows the visual display used for both the training task and the BCI task. Subjects fixated on a yellow-orange central fixation ball in the centre of the screen ((1 visual degree radius). Six degrees to the left and right on the screen, we presented two doughnut-shaped wheels (inner radius of 0.5 visual degrees; outer radius 1 degree; the center of each wheel was located 2 visual degrees below the midline).

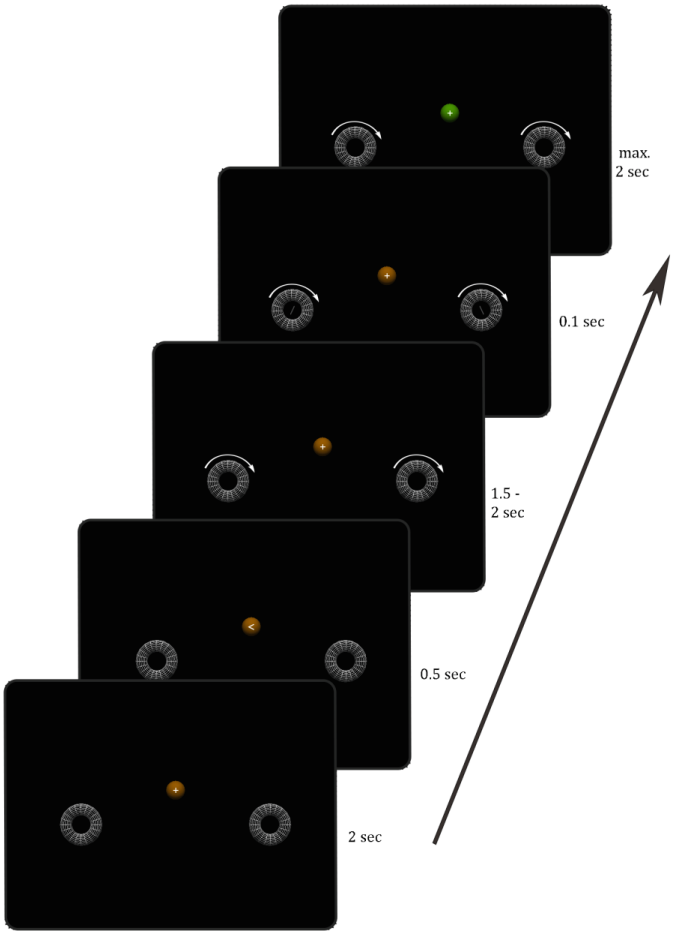


Figure 3 The visual stimuli used in the training and BCI task. Subjects were fixating on the central fixation element throughout the task. Two seconds after the beginning of each trial, a centrally presented cue (0.5 s) instructed the direction of covert attention. In the training task, the wheels rotated into a random direction with a fixed velocity for a random interval (1.5 - 2 s). Subsequently left- or right-tilted bars were shortly flashed on each side in the middle of the rotating wheels. The subject had to report the orientation of the bar on the attended side by pressing one of two buttons. The visual setup of the BCI task resembled the one of the training task, but without appearing bars. In the BCI task the direction and velocity of the wheels' rotation were determined by the outcome of the template matching classifier.

STIMULUS EQUIPMENT Stimulus presentation was performed using MATLAB and Psychtoolbox (Brainard, 1997; Pelli, 1997) and a liquid crystal display video projector (SANYO PROxtraX multiverse; refresh rate of 60

Hz), back projecting onto a screen in the magnetically shielded room using two front-silvered mirrors. The distance to the screen as well as the size of the displayed screen size was measured individually for each subject to calibrate the stimulus sizes and distances in visual degrees, ensuring the same stimulus properties across sessions and subjects.

EXPERIMENTAL PARADIGM The training task resembled a Posner-cueing task (Posner, 1980), where subjects had to fixate centrally and received a cue for 0.5 seconds instructing the side to covertly attend. After the presentation of the spatial cue, the wheels started rotating either to the left or to the right with a constant velocity of 0.3 degrees per frame (18 degrees per second). After a 1.5 – 2 s random interval, we presented vertically oriented bars in the center of both wheels for 0.1 s. The subjects' task was to identify whether the bar on the attended side was tilted to the left or to the right. They indicated the perceived tilt by pressing one of two buttons with their dominant hand. The tilt direction of the distracter bar at the unattended side was independent of the attended bar. The contrast of the presented bars was adjusted per hemifield so that on average 4 of the last 5 trials were discriminated successfully, forcing subjects to remain attentive throughout the training. The training part consisted of 96 trials (48 per hemifield). A break was introduced every 16 trials (8 per hemifield).

In the BCI task we used the same visual setup without the tilted bars appearing. In the beginning of each trial, subjects received a cue instructing them which side to attend. Subsequently the wheels started rotating in the direction of covert attention as assessed by a template matching classifier based on the templates from the training task (described in more detail below). At each update step (called a "subtrial"), the rotation velocity of the wheels was changed by 0.3 degrees per frame (18 degrees per second). If the classifier identified attention to the right side, the wheel was accelerated in the clockwise direction (or decelerated in the counter-clockwise direction). If the classifier identified attention to the left side, the wheel was immediately accelerated in the counter-clockwise direction (or decelerated in the clockwise direction). Consequently, the momentary rotation speed was the cumulative sum of the previous accelerations and decelerations in the current trial. For example, if a trial consisted of 25 subtrials, of which 15 were classified as "attention right" and 10 as "attention left" outputs, then at the end of the trial the wheels rotated by 1.5 degrees per frame (90 degrees per second) to the clockwise direction. An update was performed as fast as possible, with 2.5 +/- 0.2 (SD) classifications per second on average (0.4 s per classification). Subjects were instructed to make the wheel rotate as fast as possible to the cued direction. One trial lasted 10 seconds. The BCI task consisted of 40 trials (20 per hemifield) for each session, re-

sulting in 4033 +/- 355 (SD) classifications on average per subject. Thus, the BCI training per session was 400 s, i.e. just under 7 minutes. The attended hemifield was randomized within and across 4 blocks of 10 trials. After each trial, subjects received a scoreboard overview with their performance in the BCI task (see Figure 4).

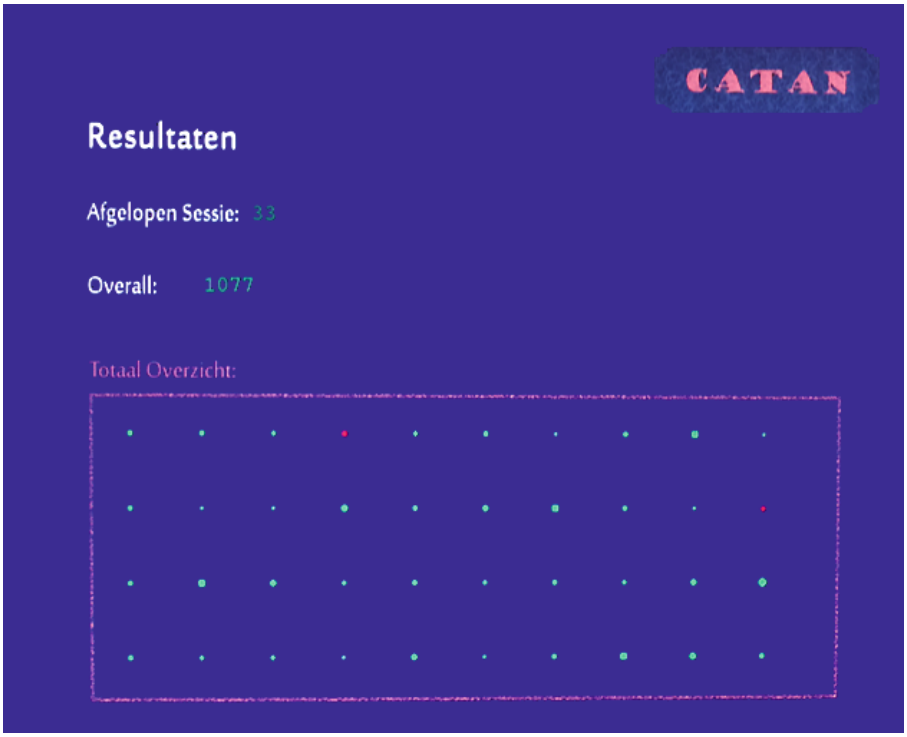


Figure 4 Example screen of the 'scoreboard' that was shown to the subjects after each of the 40 trials in a session. On top, the score of the last trial based on the rotation velocity reflecting the classification was displayed and beneath the summed score of all trials. In the bottom half, the score of the 40 individual trials of this session were shown. A green disk indicated a trial in which the wheel rotated to the cued ("correct") direction. A red disk indicated a trial in which the wheel rotated opposite to the cued direction. The size of the disks represented the final velocity, where bigger meant faster. For motivational reasons, a final velocity of 0 (thus as many correct as incorrect classifications) was indicated by a small green disk. This example scoreboard is from session three of Subject 1 with a performance of 92.5% across trials (in 37 trials out of 40 trials the wheels rotated to the correct direction – the best subject and session).

Online data analysis of the training task

For each trial of the training task we analyzed data one second before stimulus onset, i.e. one second before the vertical bars appeared. A window size of one second was chosen to achieve a spectral resolution of 1 Hz; both van Gerven et al. (2009) and Tonin et al. (2012) showed that window sizes much shorter than one second result in less reliable classification results, whereas one second of data is sufficient for a reliable estimation and classification. After the training task, but before the start of the BCI task, we computed the power spectral density of all trials of the planar gradient transformed data (see Bastiaansen and Knösche, 2000). We computed the power around individual alpha frequency band (IAF-band) of the subject in occipital sensors according to Thut et al. (Thut et al., 2006) by averaging the power spectra of all 96 training task trials. The individual alpha peak frequency (IAF) is defined as the frequency corresponding to the peak in the alpha range (8-12 Hz; Doppelmayr et al., 1998; Klimesch, 1999), and the IAF-band ranges from IAF-4 Hz to IAF+2 Hz.

SENSORS OF INTEREST Subjects had to covertly attend to the left or right hemifield during the training task. Covert attention elicits a robust lateralization pattern in the alpha-band around 10 Hz (Foxe and Snyder, 2011; Thut et al., 2006; Worden et al., 2000). We used this signal to create individual templates for attention left and attention right, respectively.

To select sensors of interest for the *left* and *right* templates for each subject, we computed the alpha modulation index (AMI) based on the IAF-band from all 96 training task trials. The AMI is defined as the relative difference between attention left and attention right trials:

$$AMI_c = \frac{\overleftarrow{\alpha}_c - \vec{\alpha}_c}{\overleftarrow{\alpha}_c + \vec{\alpha}_c}$$

Here, $\overleftarrow{\alpha}_c$ denotes averaged power in the individual alpha-frequency band of the average of all attention left trials of the planar gradient representation of MEG sensor c and $\vec{\alpha}_c$ the respective power of all attention-right trials. The AMI is stronger when alpha power is highly lateralized for attention to the left versus right hemifield, i.e. it reflects a state of high attention to the attended side (Gould et al., 2011; Haegens et al., 2011a; Thut et al., 2006; see **Chapter 2**). For each occipital sensor, we averaged the AMI over the set of adjacent sensors. Then, we stored the set s of adjacent, occipital sensors which resulted in the most positive and the most negative AMI in the training task. Eventually, we created left and right attention template, defined

as $\overleftarrow{\alpha}_s$ and $\vec{\alpha}_s$ respectively, by averaging the data of the left and right training trials at those sensors.

ONLINE DATA PROCESSING The parameters of the BCI task analysis were identical to the training phase analysis. One second after the spatial cue we analyzed the last second of MEG data, and as soon as the analysis was done we again analyzed the last second of MEG data, and so forth in a sliding window fashion (see Figure 2). The analysis of one window including transferring data over the network, testing for head and eye movements and feeding the data back to the subject took ~400 ms on average with a mean jitter of 30 ms. We used a template-matching algorithm to determine the rotation direction and speed of the wheels using the left and right attention templates $\overleftarrow{\alpha}_s$ and $\vec{\alpha}_s$ obtained from the training phase (see last section). For each subtrial *i*, we computed the IAF-band power α_{is} of the sensor set *s* by multiplying the data of the last one second with a Hanning taper and applying a Fourier transform as described above. Then, we computed the classification result as

$$C_i = \begin{cases} +1, if\,(\overleftarrow{\rho}_i - \vec{\rho}_i) > b_{t-1} \\ -1, if\,(\overleftarrow{\rho}_i - \vec{\rho}_i) \leq b_{t-1} \end{cases}$$

, where $\overleftarrow{\rho}_t$ corresponds to Pearson's correlation coefficient between the left attention template $\overleftarrow{\alpha}_s$ and the IAF-band power α_{is} of the sensors of interest in the current trial, and $\vec{\rho}_i$ the respective analogue for right attention. b_{t-1} corresponds to the correlation bias term and is described below. Thus, for each subtrial *i* we computed the difference in correlation coefficients and classified whether their difference was bigger or smaller than b_{t-1}. The classification outcome C_i was immediately written to the buffer and then read out by the stimulus PC that updated the wheel rotation (see Figure 1). Here +1 defines a classification to the left and -1 a classification to the right. The final classification of trial *t* result was determined by the summation of all classification outcomes C_i of the current trial *t*:

$$C_t = \sum_{i=k}^{n} C_i$$

, where *n* corresponds to the total number of subtrials so far and *k* is the index of the first subtrial in trial *t*. The final classification result C_t was then converted to a final score and visualized to the subject as described above (see also Figure 2). If C_t was positive, the trial was classified as "attention

left", if C_t was negative, the trial was classified as "attention right" and if C_t was zero, the trial was unclassified.

To control for systematic biases in the classification, we implemented a *correlation bias correction term*. The idea behind the *correlation bias correction term* is that on average, subjects should perform equally well for both directions. The correlation bias correction term changes the decision boundary: instead of comparing the difference of correlation coefficients with zero, we compared whether the difference was higher or lower than this bias. Therefore, we defined the correlation bias term *b* as the difference between the average correlation coefficients for all attention left and all attention right trials (including training trials):

$$b_t = \sum_{i=1}^{n} \frac{\overleftarrow{\rho}_i - \vec{\rho}_i}{n}$$

In other words, we computed the average difference in correlation coefficients for attention left and attention right over all subtrials. Note that the classification result C_t is computed using the bias term from the previous trial b_{t-1} such that the decision boundary stays constant within trial *t*.

ASSESSMENT OF ONLINE RESULTS We assessed whether subjects gain control over the feedback signal by collapsing data over all four sessions per subject and applied a binomial test. Shifts of eye gaze towards the attended side would confound the alpha power lateralization, hence we verified whether eye positions can account for the online classification rate. To test for this confound, we trained a classifier on the eye position data, and correlated the classification performance with the online results. We trained a support vector machine classifier on the data of the three eye tracker channels (horizontal and vertical eye position and pupil dilation) of the training trials of each session. Subsequently we used this classifier to classify the individual subtrials of the online BCI task. We applied the same cumulative scheme as we applied online to obtain one classification outcome for each trial, and then averaged the classification rates across sessions. In addition we computed the information transfer rate measured in bits per minute for subtrials (McFarland et al., 2003; Obermaier et al., 2001):

$$ITR = \left(\log_2(N) + P\log_2(P) + (1-P)\log_2\left({}^{1-P}/_{N-1}\right)\right) * {}^{60}/_{T}$$

The first part of the formula pertains to the number of bits transmitted per subtrial, with N as the number of possible symbols (here: N=2), P the classification accuracy and T the length of a subtrial in seconds (here: T=1).

RELATION BETWEEN CLASSIFICATION AND AMI To test whether the relation between strength of alpha lateralization predicts the individual online classification rate, we correlated the AMI with the average classification performance during the online BCI task, where the AMI is defined as the relative difference in the alpha-band for attention left and right trials for all sensors (see *Sensors of Interest*).

IMPROVEMENTS ACROSS SESSIONS We assessed whether subjects show a significant increase in online classification rate across sessions. We compared the classification performances between two consecutive sessions by one-sided paired Wilcoxon sign-rank test. Subsequently, we computed the *absolute classification bias* defined as the absolute difference between classification rates of attention left versus right trials. Note that the *absolute classification bias* is different from the *bias correction term* (see *Online data processing in the BCI task*). The *absolute classification bias* is measured as classifier performance, whereas the *bias correction term* constitutes the classifier decision boundary. We applied a linear trend analysis across sessions to assess whether the absolute classification bias systematically decreased over sessions.

VARIABILITY ACROSS SESSIONS AND TASKS In a further offline analysis, we assessed whether the pattern of hemispheric alpha band lateralization remained stable across session and tasks. Since we repositioned subjects to approximately the same head position in the MEG helmet, we were able to investigate how well the templates from a specific session generalize to the other sessions. We tested three different schemes to create templates: The o*nline templates* scheme refers to the templates we used for the online classification, i.e. those that were obtained from the Posner-cueing task conducted just before the BCI task. The *cross-session template* scheme is testing the BCI data of one session using the templates obtained from training data of the other sessions. For the *feedback-template* scheme, we tested templates obtained from the BCI data of one session and classified the BCI data remaining session. In addition, we tested whether a support vector machine (SVM) can outperform the template matching algorithm. We used the same sensor selection procedure as for the online training templates, but trained an SVM on the training data and classified data of the BCI task. For assessing similarity across these different template and classification schemes, we correlated the classification performances using (nonpara-

metric) Spearman correlations and performed paired Wilcoxon sign-rank tests on the individual classification rates per session.

3.3 Results

Assessment of online results

In the BCI task, subjects had to covertly attend to either the left or right hemifield while continuously receiving feedback about the side of attention as classified from the brain-activity. Feedback was provided by bilaterally presented wheels rotating in the direction of decoded attention (see Figure 3). Overall performance of the subjects was assessed by pooling the trials from all four sessions together. Eight out of eleven subjects performed significantly above chance level (i.e. they were able to rotate the wheels in the right direction in at least 93 out of 160 trials; $p < 0.05$; Binomial test, see Figure 5A). Two subjects achieved an average classification rate significantly above 70% (success in at least 124 out of 160 trials), which has been reported as a requirement for obtaining a subjective feeling of control (Kübler et al., 2004); however when considering the individual sessions, 7 of the 11 subjects performed at or above 70% in at least one of the four sessions (Figure 5B). The average information transfer rate (ITR) in session four is 2.0 bits/minute, with a maximum of 8.9 bits / minute for Subject 1. Overall, results show that subjects can achieve control over the BCI signal after one session of only seven minutes.

A potential concern is that subtle overt eye-movements accounted for the changes in parietal alpha power. We correlated the offline eyetracker classification results with the online template matching accuracy (see **Chapter 3.2**). We found no correlation between eyetracker classification rate and the template matching classification rate (Figure 6, $p>0.3$).

Relationship between classification result and the alpha modulation index (AMI)

Since covert visual attention elicits a well-studied alpha modulation in parieto-occipital sensors, we investigated how this related to the template matching classification performance. We asked whether the alpha power modulated by covert attention is correlated with the average classification performance during the online BCI task. Figure 7A shows the average AMI of the training phase (-1 s to 0 s relative to stimulus presentation)

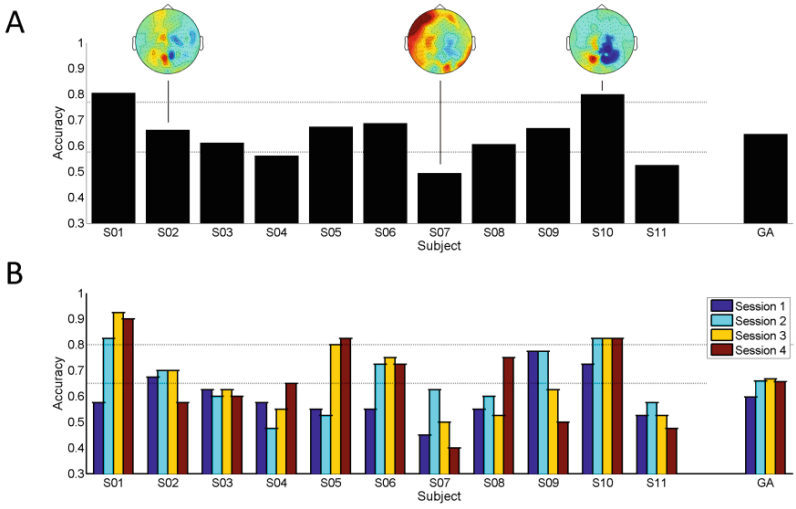


Figure 5 Classification rates per subject. The dotted horizontal bars indicate the 50% (lower one) and 70% (upper one) significance level. The GA column represents the grand-average over subjects. **A** Cumulative classification accuracy. Subject 2, 3, 5, 6, 7 and 9 perform significantly better than chance level, Subject 1 and 10 achieve a performance significantly above 70%. Example of topographic plots of the alpha modulation index in the BCI sessions are shown for three subjects (2, 7 and 10) **B** Accuracy across sessions for all subjects. Subjects 1 and 10 perform significantly better than 70% in session 2, 3 and 4. Subject 5 performs significantly better than 70% in session 4.

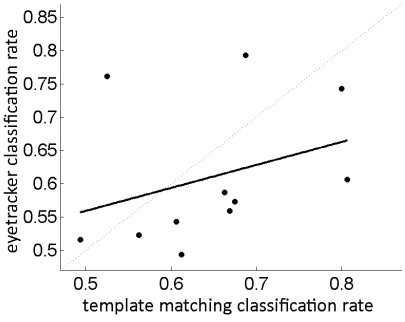


Figure 6 Correlation between offline eye-tracker classification rate and online template matching classification over subjects. There was no significant correlation (r^2= 0.1, p>0.32).

averaged over sessions and then over subjects. The topographic plot shows a relative increase in alpha power around left parieto-occipital sensors and a decrease around right parieto-occipital sensors. We correlated the average session AMI of the sensors of interest with the online classification performance over subjects (Spearman correlation) and observed a strong significant correlation between the online classification performance and

the AMI of the training trials (r^2=0.6888, p=0.0021; Figure 7B). Thus, we conclude that the classification result obtained from the template pattern classification strongly reflects the individual strength of alpha lateralization.

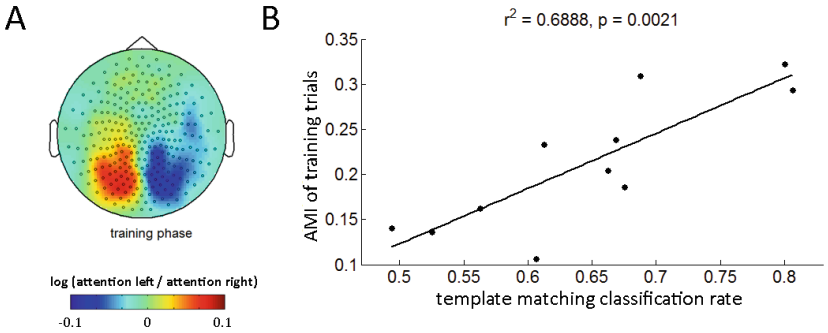


Figure 7 Alpha modulation index (AMI) averaged over subjects and the relation to the online classification performance across subjects. **A** Topography of anticipatory alpha (prestimulus) in the training trials averaged over subjects. **B** Spearman correlation between the AMI from the training trials and the online classification accuracy over subjects (r^2=0.6888, p=0.0021). A high alpha lateralization in the training task is predictive of better online control in the BCI task.

Improvements across sessions

We assessed whether subjects show a significant increase in online classification rate across sessions. On average, subjects reached significant control in the second session, but not in the first session (see Figure 5B). We compared the classification performance in the first session with the classification performance of the second session using a one-sided paired Wilcoxon sign-rank test. We found that subjects show a significant training effect (Z=-1.74, p=0.04) after session 1, but we found no significant improvement from session 2 to session 3 or 4 (all p>0.3). Subject 9 complained about tiredness and lack of focus in session three and four, resulting in a tremendous drop in classification performance from 78% in the first two sessions to 50% in the last session. Other subjects show a huge increase in classification performance not after the first, but after the second or third session (e.g. Subject 5 or 8). We conclude that subjects in general learn to control the BCI within just one session.

Subsequently, we explored what factors might have caused such an improvement. In the pilot experiments we observed a strong bias towards one side in terms of alpha lateralization, with some subjects being significantly better for attending the left compared to the right side and *vice versa*. We hypothesize that if subjects gain control over the BCI, the average classifi-

cation rate will increase and the classification bias towards one side will be reduced. Therefore, we computed the *absolute classification bias* for all subjects and each session (Figure 8), which is defined as the absolute difference between classification rates of attention left versus right trials[2]. A linear trend analysis revealed that the *absolute classification bias* dropped from 16.8% in the first session to 6.8% in the fourth session ($F(3, 30) = 3.0303$, $p<0.05$). We can conclude that as subjects learnt to control the BCI, the bias towards one hemifield was reduced.

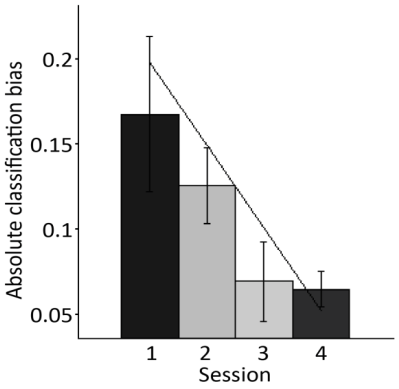


Figure 8 Absolute bias across subjects and sessions. The absolute bias is defined as the absolute difference in classification performance between the attention left and the attention right condition. The absolute bias gradually decreases from the first session to the fourth session as assessed by a linear trend analysis ($F(3, 30) = 3.0303$, $p<0.05$), showing that subjects gain better control over their alpha lateralization with increasing training.

Variability across sessions and tasks

Finally, we asked whether the hemispheric alpha band lateralization remained stable or whether it changed with the BCI training. Since we repositioned subjects to approximately the same head position in the MEG helmet, we were able to investigate how well the templates from a specific session generalize to the other sessions. Figure 9 shows the classification performance obtained applying different templates or classifiers. The templates we used for the online classification were obtained from a Posner-cueing task conducted just before the BCI task (black bars in Figure 9). We classified the BCI data of a given session when using the templates obtained from another training session (red bar in Figure 9). This cross-session classification resulted in accuracies highly correlated over subjects with the online classification results (black bars in Figure 9), in which we used the training template from the same session ($r^2 = 0.75$, $p < 0.001$). Note that although the obtained classification rates are comparable with the

[2] Note that the absolute classification bias is different from the bias correction term (see Online data processing in the BCI task). The absolute classification bias is measured as classifier performance, where the bias correction term constitutes the classifier decision boundary.

online case, for example Subject 4 shows a huge increase in classification rate from 56.25% (chance level) to 68.75% (significantly above chance level). This improvement is marginally significant (Wilcoxon paired sign-rank test, Z=1.83, p=0.07). On the grand-average level, however, we found similar classification rates (Wilcoxon paired sign-rank test, Z=-0.24, p=0.81), indicating that the training templates are exchangeable over sessions.

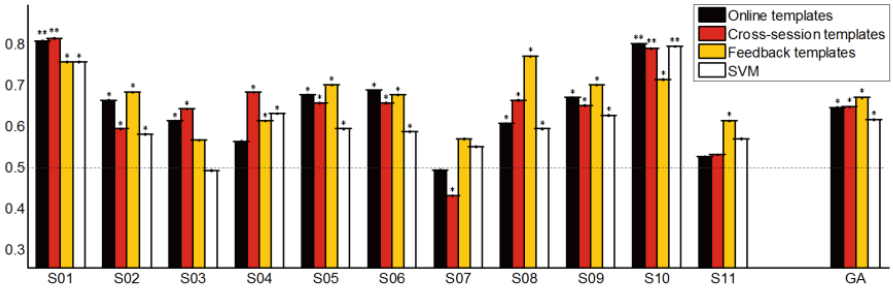


Figure 9 Classification accuracy of different classifier schemes. The black bar shows the online classification rate (i.e. reproduces Figure 5a). The red bar shows the classification rate obtained when applying a training template of one session and testing on the BCI data of the three other sessions. The yellow bar shows the classification rate obtained when creating templates from the BCI data of one session and tested on the BCI data of the three remaining sessions. The white bar shows the classification rate obtained by a SVM classifier trained on the training templates of one session and tested on data of the BCI task of that session. The GA column represents the grand average results over subjects. The horizontal bar indicates the 50% chance level. * indicates a significance from the 50% chance level and ** indicates significance from 70% accuracy. No significant interactions within subjects were found.

We also investigated whether online classification performance is influenced by the heterogeneity between the training task that the templates are created from and the BCI task. We created templates from BCI data of one session and classified the remaining sessions (Figure 9, yellow bar). Again classification rates are strongly correlated over subjects with the online classification rate (r^2 = 0.49, p=0.016). Note that Subject 11 obtains a classification performance significantly above chance, which she did not before. This improvement is, however, not significantly different from the online results (Wilcoxon paired sign-rank test, Z=1.1, p=0.27). We conclude that templates based on the BCI data result in neither significantly better nor worse classification rates (Wilcoxon paired sign-rank test, Z=-1.07, p=0.28).

Finally, we ask whether a more advanced machine learning technique, support vector machine (SVM), can outperform the template matching algorithm (Figure 9, white bar). Also here we found a strong correlation over subjects with the template matching classifier we applied online

(r^2=0.59, p=0.0059) and found no significant increase in classification performance compared to the online accuracies (Wilcoxon paired sign-rank test, Z=-1.34, p=0. 18). Summarizing, the analyses above demonstrate that classifying based on the alpha lateralization pattern is reliable and robust, independent of the classifier and remains stable across different sessions and between different experimental tasks (Posner-cueing task versus BCI task).

3.4 Discussion

In this study we demonstrated that posterior alpha power modulated by covert attention can be used as a control signal for an online brain-computer interface. This was achieved using MEG and a simple template matching approach. The classifier made use of the well-established hemispheric lateralization of alpha band power with respect to direction of covert attention. Eight out of eleven subjects were able to perform better than chance level in the online setup. Over the course of the experiment, subjects were able to increase their classification performance. We showed that improved performance over time was accomplished by reducing the individual bias towards the left of the right. Interestingly, classification accuracy was not increased by different training templates. This means that the pattern of alpha lateralization remains stable over sessions and tasks, but that the individual ability to shift and maintain attention was trained. Overall, the study revealed new characteristics about the robustness and trainability of alpha lateralization and demonstrates that it is feasibility to use posterior alpha power as an online brain-computer interface signal.

The design of our BCI paradigm is based on more than a decade of cognitive neuroscience investigation of covert attention (Foxe and Snyder, 2011; Thut et al., 2006; Worden et al., 2000). In particular these studies have demonstrated that posterior alpha activity is robustly lateralized when covert attention is directed to the left or right hemifield. Here, we show that a simple template matching approach yields performance comparable to other studies, both in terms of classification rate as well as information transfer rate per subtrial. On trial level, our paradigm yielded an average performance of around 66% in the last session, which is in between the offline studies by van Gerven et al. (2009a) and Kelly et al. (2005) and the online study by Tonin et al. (2013). On subtrial level, Subject 1 obtained a maximal information transfer rate of 8.9 bits / minute which is comparable to the maximum ITR found by Kelly et al. (7.5 bits/minute) and van Gerven et al. (8.89 bits / minute). Also, the average ITR in session four of 2.0

bits/minute is comparable to the values reported by van Gerven et al. (2009). It should be noted that the paradigms used by Kelly et al. and van Gerven et al. are not applicable for continuous control while receiving feedback. In both paradigms, cueing one side was followed by a change in visual stimulation at that side. In a real BCI setting, the attended side cannot be known beforehand; thus no stimulation at a single hemifield can occur. Tonin et al. (2013) provided discrete feedback at the end of a trial. To the best of our knowledge, our paradigm presents the first reported approach where simultaneously continuous feedback and BCI control can be achieved in a covert attention paradigm. This is a crucial aspect for a real-life application of the BCI. We conclude that posterior alpha power can be used as a brain-computer interface control signal based using a simple template matching approach.

We would like to suggest some improvements to the proposed brain-computer interfacing paradigm. First, we used rather long trials of 10s each. While this is perfectly fine for training of alpha lateralization, it is impractical for swift responses. For example, to reduce the time until a decision is made, feedback could be stopped once the cumulative evidence in favor of one of the sides exceeds a threshold. There might be individual optimal time windows to boost ITR (Tonin et al., 2012, van Gerven et al., 2009). Second, for some subjects we found that the templates obtained from the training data were not optimal to achieve significant control (Subject 4 and Subject 11). In general, a training template from the same day resulted in similar classification results when compared to a training template from any other day. However, in Figure 9 we show that individual subject could have benefitted more from other templates than the ones we used online. For 10 out of 11 subjects, we found at least one set of templates that resulted in performance significantly above chance, suggesting that there is room to improve the training template construction. Moreover, we observe that good templates can be created in a single training session and used throughout or can later extended by BCI data. Hence we could skip the training part in subsequent sessions without a significant drop in individual performance. Third, we use short training sessions of 40 trials times 10 second only, i.e. in total only 400 seconds of training data per session. It remains to be tested whether more BCI trials per session can result in better or faster subject learning. Fourth, our data shows that subjects can improve their performance after the first session. However, individual subjects showed huge increases in performance only after the third or fourth session (see Figure 5b). It remains to be tested whether training would further benefit from more than 4 training sessions, as for instance often 30-40 sessions are used in neurofeedback sessions in clinical settings

(Fuchs et al., 2003; van Dongen-Boomsma et al., 2013; Vollebregt et al., 2013). These improvements might increase usability and lead to a better user experience by faster classification results.

Further, there are a number of technical improvements that could decrease feedback delay. The main contribution to the delay between the subject's intention and the visual feedback is due to the delayed and jittered availability of the MEG data in the IPC shared memory buffer due to block size mismatch in the MEG digital processing hardware. We measured this delay to be in the range of 100-200ms. Part of the issue is caused by the online head localization, which adds a relatively coarse block-wise processing step in the MEG processing stream. Optimizing the acquisition settings might allow for some reduction in delay and jitter. Furthermore, CTF/MISL, the manufacturer of our MEG machine, recently designed new electronics that also promises a smaller delay. Reducing the feedback delay and the jitter might improve usability and efficacy of the paradigm as well. Moreover, although we show no further improvement in classification rate when using a support vector machine in contrast to the template matching algorithm, applying more advanced machine learning techniques such as common spatial patterns (Guger et al., 2000; Pfurtscheller et al., 2000), Kalman filtering (Sykacek et al., 2004) or Bayesian classifiers using priors (Lotte et al., 2007; Tonin et al., 2013) based on the current wheel rotation might increase classification accuracy. We believe that if improvements are incorporated, the user experience and classification rates will improve.

We showed that subjects using this brain-computer interface improve their ability to modulate their posterior alpha activity (see Figure 5, 7 and 8). This increased mental control might have longer lasting behavioral consequences in terms of allocating spatial attention. For example, subjects might become better at processing the attended hemifield by reducing contralateral alpha power, thereby becoming better at processing the attended stimuli. Also, subjects might become better in ignoring the unattended hemifield, which would come along with an increase in ipsilateral alpha power. Future research should aim at investigating the behavioral consequences of subjects' ability to allocate attention after such training (reviewed in **Chapter 5**). Eventually the proposed brain-computer interface control signal could for example be used in ADHD patients, who have a reduced capability of maintaining hemispheric alpha lateralization (ter Huurne et al., 2013).

3.5 Conclusion

In this study we have shown the feasibility of using posterior alpha power as a brain-computer interface control signal in a covert attention paradigm while participants received continuous feedback on their performance. Participants quickly obtained control in the setup and showed improvement during the course of the four sessions. Given the strong correlation between posterior alpha power and behavioral performance demonstrated in earlier studies, we hypothesize brain-computer interface training of posterior alpha oscillations to improve the ability to allocate and maintain spatial attention.

Chapter 4

Real-time MEG neurofeedback training of posterior alpha activity modulates subsequent visual detection performance

This chapter is based on

Okazaki, Y.*, Horschig, J.M.*, Luther, L., Oostenveld, R., Murakami, I., Jensen, O. (2015), Real-time MEG neurofeedback training of posterior alpha activity modulates subsequent visual detection performance. NeuroImage 107, 323-332. doi:10.1016/j.neuroimage.2014.12.014

*** equally contributing authors**

Abstract

It has been demonstrated that alpha activity is lateralized when attention is directed to the left or right visual hemifield. We investigated whether real-time neurofeedback training of the alpha lateralization enhances participants' ability to modulate posterior alpha lateralization and causes subsequent short-term changes in visual detection performance. The experiment consisted of three phases: (i) pre-training assessment, (ii) neurofeedback phase and (iii) post-training assessment. In the pre- and post-training phases we measured the threshold to covertly detect a cued faint Gabor stimulus presented in the left or right hemifield. During magnetoencephalography (MEG) neurofeedback, two face stimuli superimposed with noise were presented bilaterally. Participants were cued to attend to one of the hemifields. The transparency of the superimposed noise and thus the visibility of the stimuli was varied according to the momentary degree of hemispheric alpha lateralization. In a double-blind procedure half of the participants were provided with sham feedback. We found that hemispheric alpha lateralization increased with the neurofeedback training; this was mainly driven by an ipsilateral alpha increase. Surprisingly, comparing pre- to post-training, detection performance decreased for a Gabor stimulus presented in the hemifield that was un-attended during neurofeedback. This effect was not observed in the sham group. Thus, neurofeedback training alters alpha lateralization, which in turn decreases performances in the untrained hemifield. Our findings suggest that alpha oscillations play a causal role for the allocation of attention. Furthermore, our neurofeedback protocol serves to reduce the detection of unattended visual information and could therefore be of potential use for training to reduce distractibility in attention deficit patients.

4.1 Introduction

Attention is a remarkable ability of the human brain ensuring that precious neural resources are allocated to sensory input related to our current goals and needs. Allocation of attention is an outcome of biased competition between increased activity for attended objects and reduced activity for non-attended objects (Desimone and Duncan, 1995; Kastner et al., 1998). Recent human MEG and EEG studies have suggested that sensory gating is achieved by adjustment of oscillatory alpha activity. Brain regions that are activated during a task exhibit low alpha power (Klimesch et al., 1997), whereas regions associated with task irrelevant and potentially interfering processes exhibit relatively high alpha power (Jokisch and Jensen, 2007; Sauseng et al., 2009; Worden et al., 2000). During covert attention, concurrent increased alpha power in the ipsilateral hemisphere and decreased alpha power in the contralateral hemisphere with respect to the attended direction have been found (Kelly et al., 2006; Rihs et al., 2007; van Gerven and Jensen, 2009; Worden et al., 2000; Yamagishi et al., 2003). As hypothesized, the strength of the hemispheric alpha lateralization correlates with participants' performance, in terms of both reaction times and accuracy (Kelly et al., 2009; Thut et al., 2006). This correlation between alpha lateralization and perception implies that perceptual sensitivity might change if alpha lateralization can be increased by training covert visual spatial attention. We tested this hypothesis in an online neurofeedback paradigm. Participants received feedback in real-time controlled by the posterior alpha lateralization.

Brain-computer interfacing (BCI) and neurofeedback are techniques to feed back some aspect of neural activity to the participant with the aim that the participant gains control over the fed back aspect of neural activity. In invasive BCI studies, monkeys were able to quickly manipulate the degree of motor neuron activity, when their neural activity was continuously represented as a cursor movement on a computer screen (Serruya et al., 2002; Taylor et al., 2002). In humans, Ros et al. (2010) showed that the intrinsic suppression of alpha oscillation during neurofeedback leads to changes in the motor-evoked potentials elicited by transcranial magnetic stimulation of the primary motor cortex. Recently, human non-invasive BCI studies showed evidence that changes in neural activity by neurofeedback training can cause behavioral changes. For example, it has been shown that neurofeedback of theta oscillations increases working memory capacity in the elderly (Wang and Hsieh, 2013). Furthermore, Shibata et al. (2011) demonstrated that early visual areas are sufficient to cause visual perceptual learning. Using fMRI neurofeedback, they trained participants to induce a

BOLD signal pattern in early visual areas, similar to the activity elicited during visual stimulation of specific orientations of a target stimulus. This neurofeedback training was performed without concurrent visual presentation of the specific, trained target orientations. The enhancement of the BOLD signal pattern independent of visual stimulus presentation resulted in improved perceptual sensitivity of the specific, trained target orientations. Neurofeedback techniques using neuronal oscillations have shown promise in the past, e.g. in treatment of attention disorders in ADHD patients (Arns et al., 2014, 2009; Lubar et al., 1995). However, the reliability of these findings is under constant debate (van Dongen-Boomsma et al., 2013; Vollebregt et al., 2013). This motivates investigations of more basic consequences of neurofeedback.

The present study used an MEG neurofeedback paradigm in which participants were trained to enhance alpha lateralization in posterior regions by covertly attending to either the left or to the right visual hemifield. We compared two groups: one group received real-time neurofeedback (neurofeedback group) and the other group received sham feedback (sham group). We hypothesized that only the neurofeedback group would show a change of posterior alpha lateralization. Furthermore we trained participants in one visual hemifield and tested the behavioral consequences for visual detection. If alpha lateralization is involved in attentional gating, the training should result in a change in visual detection performance. Here, we tested whether participants of the neurofeedback group could increase their alpha lateralization by neurofeedback training and whether such training affected detection performance in a subsequent visual detection task. If these hypotheses were confirmed, our study would provide supporting evidence for a causal link between posterior alpha lateralization and visual detection performance.

4.2 Materials and Methods

Participant groups

40 healthy right-handed Caucasian participants (20 female, 20 male, 18-33 years of age) gave informed, written consent to participate in the study after the protocol was explained to them. The study was approved by the local ethics committee (CMO region Arnhem / Nijmegen). In a double-blind fashion participants were randomly divided into one of two groups, the neurofeedback (n = 20, 10 male, 10 female) or the sham group (n = 20, 10 male, 10 female). The participants of each group were further split into two equal-sized subgroups that were trained during the neurofeedback task (Figure 2A) on attention to the left hemifield or to the right hemifield,

respectively. The recordings of four participants (two males and one female in the neurofeedback group and one female in the sham group) were aborted due to MEG system hardware failures, so data from the 36 remaining participants were used for offline analysis. The participants in both groups were provided with identical verbal and written instructions, which explained that paying greater attention to the instructed hemifield would result in improved visibility of the facial stimuli.

Data acquisition

We measured brain activity using a whole head magenetoencephalography (MEG) system with 275 axial gradiometers (Omega 2000, VSM MedTech Ltd., Coquitlam, B.C., Canada). Eye movements and blinks were monitored using an EyeLink 1000 eye-tracker (SR Research, Ontario, Canada). Head position with respect to the sensor array was continuously computed by three localization coils fixed at anatomical landmarks (nasion, left and right ear canals). Stimulus delivery was controlled by Psychtoolbox-3 (Brainard, 1997; Pelli, 1997). Gamma correction was applied to ensure linear luminance stimulus characteristics. Real-time processing and all offline analysis were done using FieldTrip (Oostenveld et al., 2011), an open source MATLAB (Mathworks, Natick, MA, USA) toolbox for the analysis of neurophysiological data.

Online neurofeedback

We designed a closed-loop feedback system making it possible to analyze the recorded brain activity in real-time (Figure 1). MEG, head-coil and eye-tracker data were written by the CTF acquisition software to an IPC shared memory segment on the acquisition computer and subsequently copied by the FieldTrip software to a TCP network accessible buffer as soon as possible (Jensen et al., 2011). The FieldTrip buffer is accessible concurrently from the acquisition and the real-time classification computers. Data were down-sampled from 1200 Hz to 200 Hz, after applying filters (low-pass; 50 Hz, notch; 50 Hz), and the synthetic 3rd order gradient was applied to eliminate environmental noise before streaming data to the buffer. The feedback delay and jitter varied between 100 – 200 ms, which we measured as the time it takes from sending a trigger from the stimulus computer to the acquisition computer and sending a trigger back based on processed data via the classification computer.

The classification computer acquired not only MEG data from the buffer, but also external data, i.e. the trigger signal for event timing, the eye-tracker data and head localizer coil positions. Once an event trigger was

detected, data were read from the buffer to compute alpha power (8.0 – 12.0 Hz), which was computed from a 1 s data segment immediately preceding the trigger (timing of event trigger is schematically indicated by red dashed line in Figure 2B and 2C), i.e. the interval in which participants had shifted their attention to the cued direction (see **Chapter 4.2** *Overall procedure)*. Eye movement and head position were monitored online (Stolk et al., 2013). When an eye movement exceeded 3.0° and/or a head movement exceeded 5 mm, the data were discarded from further analysis and the participant was alerted by a change in fixation cross color (blue for an eye movement and red for a head movement). In case of excessive head movement, we realigned the participant to his/her initial head position.

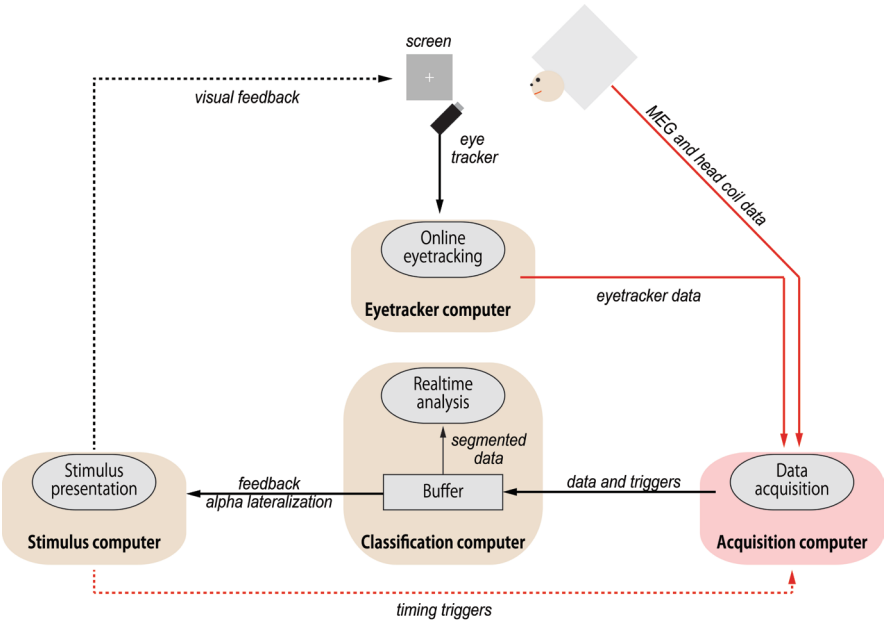


Figure 1 A schematic illustration of real-time neurofeedback. All data (red line), including head-coils, eye-tracker and event trigger data, are written to a limited, locally shared memory and copied to a TCP/IP accessible data buffer. Event trigger is continuously monitored by "real-time analysis client" running on the classification computer. Once a trigger is detected, the data are read from the buffer to compute the z-transformed alpha lateralization index (zALI) of the predefined sensors. This zALI value was immediately transferred to the stimulus computer and the visual feedback was adapted according to this value.

Overall procedure

The experiment consisted of three phases within 1 hour (Figure 2A): (i) pre-training phase (~15 min), (ii) neurofeedback phase (~10 min) and (iii) post-training phase (~15 min). In the pre- and post-training phases, the

detection threshold for a Gabor stimulus was determined independently for the left and the right hemifield. This detection threshold is considered a measure for the ability to allocate spatial attention. The pre-training task was also used for selecting the sensors that are most sensitive in showing alpha-band (8.0 – 12.0 Hz) effects related to covert attention. In each of the three of phases, the stimuli sizes were 7.0° (measured in visual degrees) and they were presented at 70° eccentricity on a uniform gray background.

Pre- and post-training phases

The contrast threshold for a Gabor grating stimulus (standard deviation of the Gaussian envelope, 1; spatial frequency, 3.5 cpd; orientation, 45°) was determined independently for the left and right hemifields. The stimulus contrast varied from trial to trial according to the **Ψ**-method, which is an adaptive Bayesian method to measure the threshold and slope of the psychometric function (Kontsevich and Tyler, 1999). The threshold was determined using 60 trials per attended hemifield. A trial started with the presentation of a cue indicating the side of stimulus presentation for 0.5 s, followed by a 1.2 s anticipatory interval. Subsequently the Gabor stimulus was presented in the cued hemifield for 0.05 s in one of the two intervals followed by the presentation of a random-noise mask for 0.05 s in both hemifields (left and right) and intervals (first and second). The intervals were separated by 0.5 s. The participants were then asked to indicate if the stimulus was presented in the first or the second interval using a two-alternative forced choice task. They had to respond with the index or middle finger of their dominant hand for respectively the first or the second interval. See Figure 2B for a schematic overview.

Sensor selection

At the end of the pre-training phase, we computed the alpha modulation index: $AMI_s = \log_{10}\left(\alpha_{s(Lc)}/\alpha_{s(Rc)}\right)$, where $\alpha_{s(Lc)}$ and $\alpha_{s(Rc)}$ refer to the average alpha power during the 1 second anticipatory interval of all left and right cued trials per MEG sensor (s), respectively. Based on the topography of the participant-specific AMI, we selected 5 left and 5 right parieto-occipital sensors with the respectively most positive and most negative AMI, as illustrated for a representative participant by the white dots in Figure 2B.

Neurofeedback phase

We used images of five different faces (Tanskanen et al., 2005) and their scrambled images. The scrambled face images were generated by randomizing the phase angle obtained from the Fourier transform of the original

face image so that their mean luminance and spatial frequencies remained identical. In the neurofeedback group, the visibility of the face superimposed upon the scrambled face was varied according to the momentary extent of posterior alpha lateralization (see **Chapter 4.2** *Visibility of the faces*).

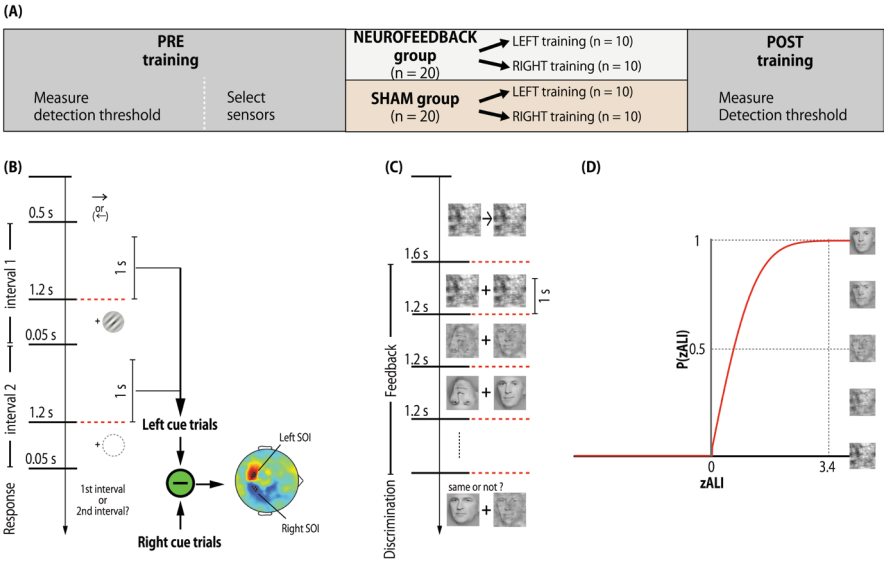


Figure 2 A Flow chart of the three task phases: pre-training, neurofeedback-training and post-training phase. Participants were randomly assigned to the neurofeedback or to the sham group, and further assigned to either the left or the right training group. B Procedure of the pre- and post-training phase. A detection threshold using two-interval-forced-choice task was measured. A trial started by a cue (left or right arrow) instructing which hemifield stimulus will be presented. A Gabor grating was presented for 0.05 s at the cued (attended) location in one of two subsequent intervals. Participants had to report which interval contained the visual stimulus by pressing one of two buttons. At the end of this phase, we selected sensors from the contrast left minus right cued trials. White dots in the topographic representation depict sensors of interest (SOIs) for left and right hemisphere. C Procedure of the neurofeedback phase. The participants were instructed to keep attention to the cued hemifield (same hemifield throughout the whole phase). The instantaneous zALI was continuously used to modulate the visibility of a face image. Thus participants were trained to bias alpha lateralization to the attended direction. (D) Relationship between face visibility and alpha lateralization. Using the mean and standard deviation of the alpha lateralization from the pre-training phase, we computed the cumulative probability distribution of the z-scored ALI per participant (zALI). Only positive zALI values resulted in a visible face, where a zALI higher than 3.4 resulted in a 100 % visible face.

The neurofeedback phase was composed of 20 blocks, and in each block there were 10 feedback trials. The structure of a neurofeedback block is schematically illustrated in Figure 2C. Participants were instructed to keep covert attention to either the left or right hemifield throughout the whole

neurofeedback phase. Participants were explained that the level of attention would determine the face visibility, i.e. greater attention would lead to a clearer face image during a block, and also that the average level of attention throughout the trials would determine the difficulty of the face discrimination task at the end of every block. Each block started with a spatial cue presented centrally and with bilateral presentation of fully scrambled faces (i.e. 0% visible) for 1.2 s. Subsequently, participants had to adjust the visibility of the faces in the 10 feedback trials of that block. Feedback was provided every 1.2 s according to the alpha lateralization of the last 1 s, thus a neurofeedback block took 12 s (see Figure 2C). Bilaterally presented faces were identically and equally adjusted in visibility but the one presented at the unattended side was presented up-side-down to reduce distraction. In the sham group, the visibility of the face was determined by the participants' alpha lateralization from a pseudo-randomly chosen trial of the neurofeedback phase, i.e. a high alpha lateralization was still rewarding, but was not necessarily immediately fed back to the participant.

In the discrimination task at the end of every block, two faces were presented bilaterally: a fully visible face and a "scrambled hybrid-face", which was an intact face superimposed with a scrambled face. The visibility of the hybrid-face was determined by the mean alpha lateralization during this block, i.e. the lower the alpha lateralization was in the 10 feedback trials the noisier the hybrid-face was. Participants had to identify whether the two faces were from the same person. Note that the face presented during the feedback was different from the faces presented in the discrimination task. This ensured that participants were engaged in enhancing the visibility of the target face by changing the extent of covert attention and not by memorizing the identity of the face during the neurofeedback block.

Visibility of the faces

Visual neurofeedback, which reflected the level of ongoing and sham alpha lateralization, was provided to the participants of the neurofeedback and sham groups, respectively. In each feedback trial, the ratio of the contrast of the scrambled face to that of the intact face was varied according to the alpha lateralization index of the last 1.0 s for the neurofeedback group and from a pseudo-random 1.0 s interval for the sham group. The alpha lateralization index was defined as $ALI = \log_{10}(\alpha_{Is}/\alpha_{Cs})$, where α_{Is} and α_{Cs} refer to the mean alpha power recorded from the selected sensors ipsilateral and contralateral to cued attention side respectively (see **Chapter 4.2** *Sensor selection*).

The visibility of the faces was manipulated by superimposing the intact face with the scrambled face dependent on the alpha lateralization index. For the current trial *i*, we computed the *z*-scored ALI (zALI$_i$) by standardizing the ALI$_i$ with the mean and standard deviation of the ALI from all trials of the pre-training phase. We used a cumulative standard distribution function to convert the zALI to a value between 0 and 1(Figure 2D):

$$P_i(zALI_i) = \begin{cases} 1, (if\ zALI_i > 3.4) \\ 2\int_{-\infty}^{zALI_i} \frac{1}{\sqrt{2\pi}} e^{-z^2/2}\, dz - 0.5, \quad (if\ 3.4 > zALI_i > 0) \\ 0, \quad otherwise \end{cases}$$

Only a positive zALI, which reflects attention to the cued hemifield, results in values for P$_i$ above 0. A negative zALI reflects attention to the un-cued hemifield and results in $P_i = 0$. The visibility parameter V_i was computed by a smoothed average of the P$_i$'s of the last three trials as:

$$V_i = \begin{cases} \sum_{j=0}^{M-1} w_j P_{i-j} & (i \geq 0) \\ 0 & (i < 0) \end{cases}$$

with weights:

$$w_0 = {}^1/_2\,;\ w_1 = {}^1/_3\,;\ w_2 = {}^1/_6$$

Thus a high zALI led to a clearly visible face, and a low zALI led to a poorly visible face. The smoothing procedure avoids transient fluctuations of the feedback and effectively implements a low-pass filter. The weights are designed to add up to exactly 1, thereby resulting in values for V_i between 0 and 1. Finally, the visibility of the intact face was determined by $V_i I_{intact\ face} + (1 - V_i) I_{scrambled\ face}$, where I represents the image matrix of the (intact or scrambled) face.

Statistical assessment

We assessed whether participants were able to modulate the alpha lateralization in trials during the neurofeedback blocks by a Dunnett's test, which inherently corrects for multiple comparisons (Dunnett, 1955). Further, we assessed whether participants were able to significantly increase their alpha lateralization at the end of the neurofeedback training compared to the

beginning of the neurofeedback training. The neurofeedback training effects on the change in alpha were assessed using a 2x2 ANOVA with feedback-type (neurofeedback and sham) and training-hemifield (left and right) as fixed factors. In addition, we assessed whether the neurofeedback training affects the detection threshold by a 2x2 mixed design ANOVA with feedback-type (neurofeedback or sham) as a between-subject factor and with stimulus-hemifield (trained or untrained) as a within-subject factor. Simple main effect test was performed when an interaction between two factors was significant.

4.3 Results

The experiment consisted of three phases including breaks that were completed within 1 hour: (i) pre-training phase (~15 min), (ii) neurofeedback phase (~10 min) and (iii) post-training phase (~15 min). In the pre- and post-training phases, we measured the visual detection threshold. In the pre-training phase we also measured the participants' posterior alpha modulation induced by spatial shifts of covert attention. In the neurofeedback task, participants were divided in two groups and trained to attend either the left or the right hemifield. We investigated whether training of hemispheric alpha band lateralization by neurofeedback resulted in changes in detection threshold.

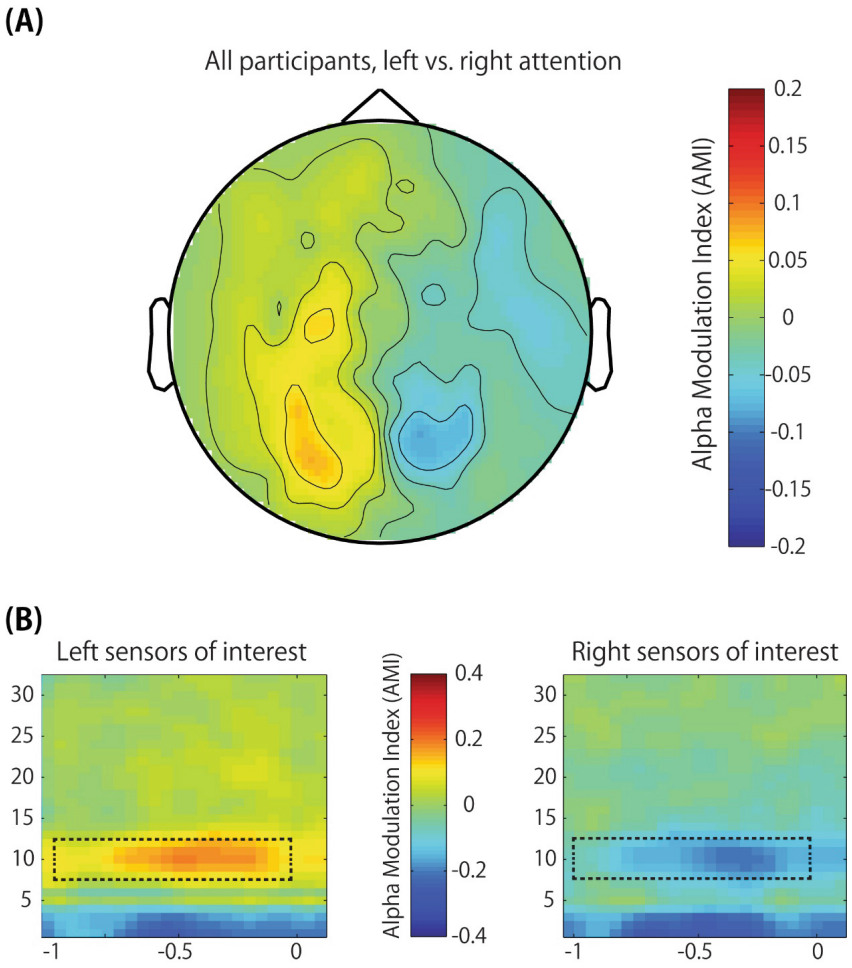


Figure 3 A Grand averaged topography of alpha modulation when participants attend to left and right in the pre-training phase. Both neurofeedback and sham group showed clear alpha modulation before presenting the Gabor gratings. B Time-frequency illustration of ipsi- and contralateral sensors of interest in the pre-training phase. The alpha lateralization increases in anticipation of the stimulus (-1 s to 0 s). The dotted box marks the time-frequency range for of our analysis.

Selected sensors in the pre-training phase

By contrasting attention left and attention right trials, we observed an alpha modulation mainly in the occipito-parietal sensors. We selected five sensors in each of the left and right hemispheres for each participant that maximized the individual alpha modulation index as a presumed neural correlate of attention (see Figure 2 and **Chapter 4.2** *Sensors selection*). These sensors were used to compute the alpha lateralization in the

neurofeedback phase. The selected sensors showed an ipsilateral alpha power increase and a contralateral alpha power decrease with respect to the attended hemifield (Figure 3A). This alpha lateralization gradually increased in anticipation of the grating stimuli in the visual detection task (Figure 3B). We conclude that the hemispheric alpha lateralization as reported in numerous studies is reproduced with the detection threshold paradigm.

Neurofeedback training effect on the alpha lateralization

We first set out to confirm that the participants in the neurofeedback group were able to manipulate their alpha lateralization based on the visual feedback during the individual neurofeedback blocks. Figure 4A shows the average change of alpha lateralization across blocks within trials. Towards later trials in a block, the alpha lateralization increases for the neurofeedback group that was trained on attention left ($p < 0.05$, Dunnett's test). No such modulation was prominent for the sham group or the right training group. We further quantified this by comparing the average alpha lateralization in the last two trials of a block using a 2x2 ANOVA with the factors feedback-type and training-hemifield. We found a significant main effect of feedback ($F(1, 31) = 4.61$, $p < 0.05$), indicating that only the neurofeedback group was able to significantly increase their alpha lateralization. We also found a significant effect of hemifield ($F(1, 31) = 7.07$, $p < 0.01$) and an interaction between these two factors ($F(1, 31) = 5.75$, $p < 0.05$; Figure 4B). Simple main effect tests revealed that the change in alpha lateralization of the left neurofeedback group was significantly larger than in the right neurofeedback group ($F(1, 31) = 12.34$, $p < 0.01$) and than in the left sham group ($F(1, 31) = 10.09$, $p<0.01$). There was no difference between the right neurofeedback and the right sham group ($F(1, 31) = 0.03$, *ns*), and also not between left and right sham groups ($F(1, 31) = 0.08$, *ns*). We conclude that, while the left neurofeedback group was able to gain control in the neurofeedback setup, this was not the case for the right neurofeedback group or the sham groups.

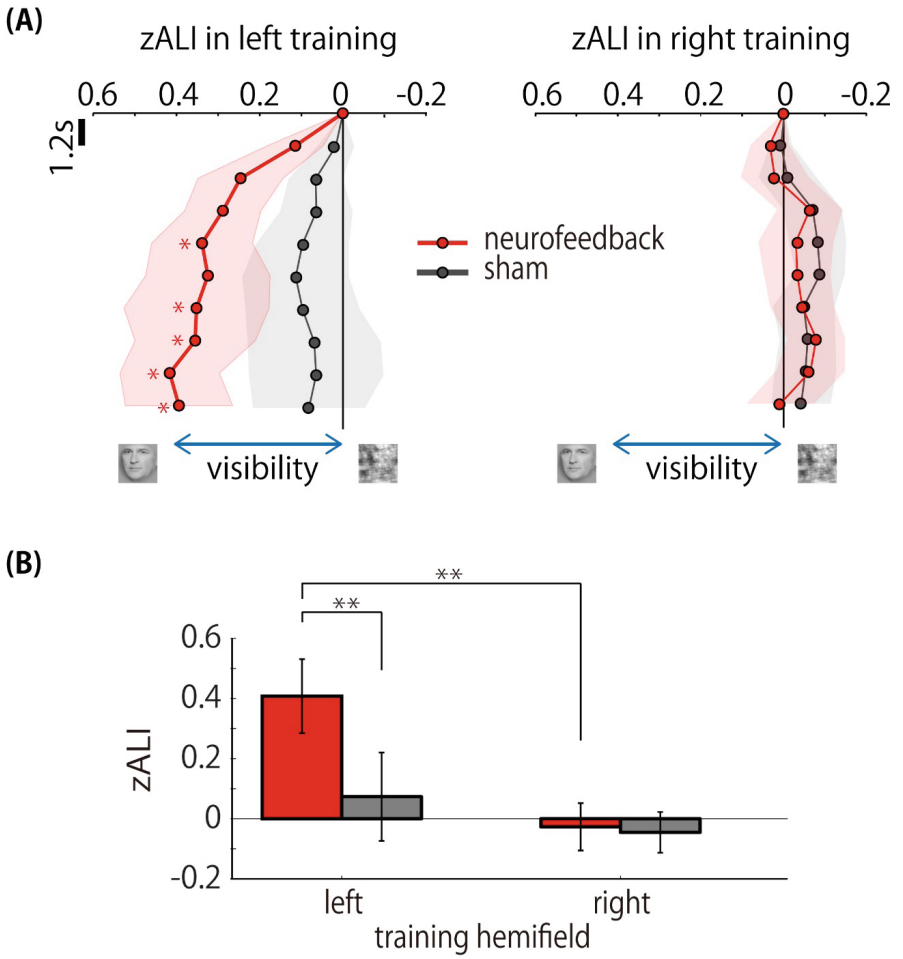


Figure 4 The change of alpha lateralization during the neurofeedback block. A The average z-scored ALI (zALI) of the ten trials in the feedback blocks. All twenty blocks were averaged and the shaded area indicates the standard deviation. The left neurofeedback group systematically increased their alpha lateralization to the left attention side (* $p < 0.05$, Dunnett's test). B The average of the last two trials of the feedback blocks. There is a significant interaction between feedback type and training-hemifield ($F(1, 31) = 5.746$, $p < 0.05$). The left neurofeedback group was able to increase their alpha lateralization during the neurofeedback blocks, which is significantly different from the modulation that could be achieved by the left sham group (** $p < 0.005$), the right neurofeedback group (** $p < 0.005$). Error bar: STD.

Next we asked whether the participants' alpha lateralization towards the end of the neurofeedback training was higher than in the beginning of the training. We compared the average magnitude of the zALI of the last five neurofeedback blocks with the first five neurofeedback blocks (*ΔALI = last – first,* Figure 5A) using a 2x2 ANOVA with the factors feedback-type and

training-hemifield. Albeit main effects were absent (hemifield: $F(1, 31) = 0.02$, *ns*; feedback-type: $F(1, 31)=1.44$, *ns*), we found a significant interaction ($F(1, 31) = 4.88$, $p < 0.05$). A simple main effect test revealed that only the left neurofeedback group was able to significantly modulate their alpha lateralization compared to the sham group ($F(1, 31)=5.67$, $p < 0.05$). This indicates that real-time neurofeedback served to enhance alpha lateralization but only when trained in the left hemifield.

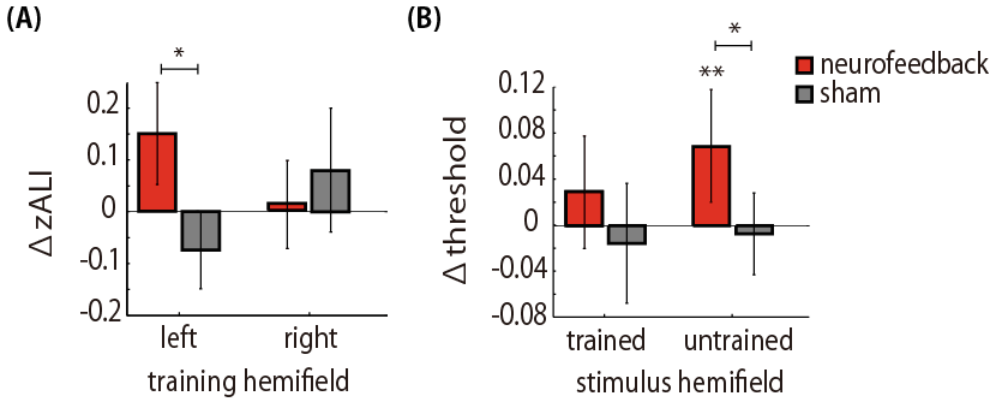


Figure 5 Training effect in the alpha lateralization and the detection threshold. A The difference in zALI between the first five blocks and last five blocks (∆zALI). The ∆zALI in the neurofeedback group was significantly larger than the one in the sham group for the left training group (* $p < 0.05$). B The difference in detection threshold between pre- and post-training phase (∆threshold). The threshold significantly increased in the neurofeedback group when the stimulus was presented in the untrained visual hemifield (** $p < 0.01$), e.g. participants who trained left attention got worse at detecting stimuli in the right visual field. This ∆threshold for the untrained hemifield was significantly different from the sham group (* $p < 0.05$). Error bar: STD.

Neurofeedback training increases the contralateral detection threshold

For the training effect on behavioral performance, we compared the detection threshold measured in the pre-training phase with the threshold measured in the post-training phase (*Δthreshold = post - pre*), see Figure 5B. We hypothesized that the detection threshold would change in the post-training phase compared to the pre-training phase specifically for the neurofeedback group. We applied a mixed 2x2 ANOVA with the factors feedback-type and stimulus-hemifield. We found a main effect (between subjects) for feedback-type ($F(1, 33) = 4.43$, $p < 0.05$), indicating that the neurofeedback group generally increased the detection threshold, i.e. got worse at the detection task, whereas it was unaffected by sham feedback. There was no significant main effect for stimulus-hemifield ($F(1, 33) = 3.16$,

$p = 0.09$) or the interaction between factors ($F(1, 33) = 1.34$, $p = 0.26$). Ad-hoc t-tests revealed that the threshold increased in the untrained hemifield in only the neurofeedback group ($t = 2.81$, $p < 0.01$, two-tailed paired t-test). Moreover, in the untrained hemifield the contrast difference between the neurofeedback and sham group was also significant ($t = 2.65$, $p < 0.05$, two-tailed unpaired t-test). We did not find a decrease in detection threshold in the trained hemifield when comparing the neurofeedback to the sham group ($t = 1.30$, $p = 0.202$, two-tailed unpaired t-test). We conclude that neurofeedback training results in decreased detection performance in the untrained hemifield. Specifically, when participants were trained in the left hemifield, visual detection became worse in the untrained right hemifield but did not become better in the trained left hemifield.

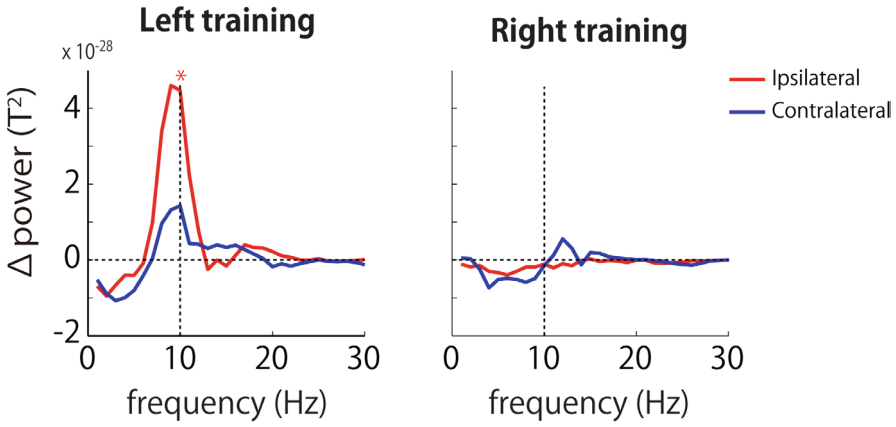


Figure 6 Training effect for ipsi- and contralateral sensors in all frequency bands, i.e. difference in power between the first five and the last five blocks. Left panel: For the left neurofeedback training group we observed a high peak in the alpha range in ipsilateral sensors, i.e. significantly more than 0 at 10 Hz (* p < 0.05), while there were no other peaks in the frequency spectrum. Right panel: For the right neurofeedback training group, there are no clearly visible peaks.

Neurofeedback training effect is specific to changes in the alpha-band

The alpha lateralization index corresponds to the ratio between ipsi- and contralateral alpha power to attended direction. Thus the increased alpha lateralization found in the test group could reflect either an increase in ipsilateral alpha power, a decrease in contralateral alpha power or a combination of both. Furthermore, to rule out that the observed behavioral effects in the neurofeedback group can be attributed to other frequencies than alpha, we computed the power spectra over the sensors of interest analogously to the previously described analyses. Figure 6 shows that there are no other clearly visible peaks in the frequency spectra as a training effect besides those around the alpha-range. Particularly ipsilateral alpha

power in left neurofeedback training group was significantly more than 0 at 10 Hz ($t = 2.37$, $p < 0.05$, two-tailed paired t-test). This indicates that the observed effects of the left neurofeedback training group can be attributed to changes in alpha power in the ipsilateral hemisphere.

4.4 Discussion

Here, we presented a neurofeedback study in which participants were instructed to keep attention to either the left or right hemifield while receiving neurofeedback on the magnitude of the alpha lateralization. The left hemifield neurofeedback training group significantly increased their alpha lateralization compared to the left hemifield sham group. We investigated whether neurofeedback of alpha lateralization had consequences for detection performance. We compared the detection threshold between the pre- and post-training phase. We found that the threshold of the neurofeedback compared to the sham group significantly increased, i.e. performance got worse, when the stimulus was presented in the untrained hemifield. These findings led us to conclude that the detection becomes worse in the untrained hemifield in response to neurofeedback training. These changes in terms of alpha lateralization and detection threshold were caused by only 10 minutes of neurofeedback training per participant.

Alpha oscillations are causally involved in cognition

The present findings speak to a causal involvement of posterior alpha oscillations in cognition and gating of information. Previous electromagnetic brain stimulation studies have shown that it is feasibility to entrain alpha oscillations (Neuling et al., 2013; Thut et al., 2011a, 2011b), and that 10 Hz entrainment results in behavioral changes (Neuling et al., 2012; Romei et al., 2010, 2008). The relevance of the here presented neurofeedback approach in studying the role of causality of alpha oscillations on human cognition is comparable to other approaches. In the present study the left neurofeedback group was able to increase alpha lateralization through an increase in ipsilateral alpha-power rather than decrease in contralateral alpha-power (Figure 6). Furthermore, only the neurofeedback training led to a significant change in behavioral performance decrease in the untrained hemifield (Figure 5). These findings are in line with the idea that posterior alpha power reflects active suppression of task irrelevant processes for allocation of neural resource (Bonnefond and Jensen, 2012; Foxe and Snyder, 2011; Jensen et al., 2002; Jokisch and Jensen, 2007; Klimesch, 1999). We conclude that by increasing alpha power ipsilateral to the attended hemifield during neurofeedback training, processing of information in the unattended hemifield became suppressed, negatively

impacting the detection of stimuli in that hemifield. This mechanism becomes beneficial when there is a need to suppress distracters in that hemifield.

Additional assessment of the relation between performance and alpha lateralization showed that participants who showed an increase in alpha band lateralization were more likely to show a change in performance (see Supplementary Figure 1). In our neurofeedback paradigm the power at other frequencies was not affected. It should be mentioned, however, that neurofeedback effects on behavior have also been achieved in other frequency bands. For example, recently it was shown that neurofeedback of theta oscillations increases working memory capacity in the elderly (Wang and Hsieh, 2013). Thus, neurofeedback of other frequency could potential also lead to behavioral modulations (reviewed in Gruzelier, 2013 and see **Chapter 5**). Thus, further neurofeedback studies using other frequency bands are required to investigate whether the performance changes in attention tasks are exclusively achievable by alpha neurofeedback.

The absence of threshold changes in the trained hemifield

The detection performance at the trained hemifield did not change. It is possible that our training paradigm might have been too short to improve basic visual skills like contrast detection; in perceptual learning studies such improvements are generally not that large (Dosher and Lu, 2005; Sowden et al., 2002) or even absent (Dorais and Sagi, 1997; Maehara and Goryo, 2007). Thus extensive long-term training might be necessary as indicated by results showing improved detection threshold in video gamers (Li et al., 2009). The null-finding for the detection threshold change is corroborated by an absence of change in contralateral alpha power relative to the trained hemifield (see Figure 6). Monkey neurophysiological studies found that a reduction in alpha power in task relevant regions in response to an attended target stimulus results in increased efficacy of stimulus processing (Buffalo et al., 2011). Our neurofeedback setup caused only ipsilateral alpha power changes, hence affecting the visual stream to the untrained hemifield. While future investigations focusing on behavioral consequences of only ipsi- or contralateral alpha neurofeedback are thus necessary to clarify the hypothesized advantage of a contralateral alpha decrease, we do provide strong support in favor of the idea that ipsilateral alpha increase results in reduced perceptual processing of the contralateral hemifield.

Differential effects for left and right hemifield training group

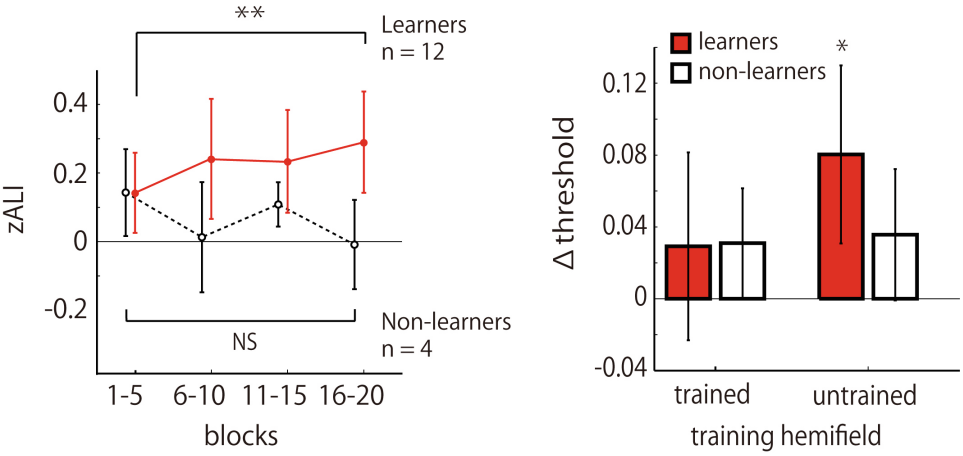
Although we found training effects of both alpha lateralization and detection threshold in the left hemifield training group, only minor training effects were observed in the right hemifield training group. The explanation for this is not immediately obvious. Participants were pseudo-randomly assigned to the left or right hemifield training group. In the pre-training phase, the initial alpha modulation of the grand averaged topography in the right hemifield training group was not as spatially defined as in the left hemifield training group (see Supplementary Figure 1), though the magnitude of alpha lateralization between the groups was not significantly different (see Supplementary Analysis). Thus the relatively less organized alpha lateralization in the right hemifield training group is not the principal cause for the weak training effects of the right training group by neurofeedback learning.

Alternatively, the observation in our study could reflect a basic property of visual attention, i.e. a difference in parietal function between hemispheres during covert visual spatial attention. It has been proposed that the right hemisphere contributes to directing attention to either left or right visual field, while the left hemisphere contributes to the directing attention to the right hemifield only (Mesulam, 1999; Pouget and Driver, 2000). This results in asymmetric effects of parietal lesions in patients, where left parietal lesions result in little deficit in direction of visual spatial attention (owing to compensation by the right hemisphere), but right parietal lesions result in hemi-spatial neglect on the left (Heilman and Van Den Abell, 1980; Vallar and Perani, 1986). Alpha lateralization neurofeedback in the right hemifield training group might be unsuited, as it is ineffective to suppress input from only the untrained (i.e. unattended) hemifield but might suppress input from both hemifields. In terms of a hemispheric asymmetry, we recently found that alpha modulation in the right hemisphere did not operate to suppress distracter in the unattended hemifield (Okazaki et al., 2012). Thus in the here presented study, an ipsilateral increase in alpha power in the right hemifield training group would not have been beneficial for suppressing the untrained hemifield. It will be crucial in future studies to increase our knowledge of the specific contributions of alpha oscillations, asymmetric hemispheric effects and associated neural networks. The outcome of such studies in turn would increase our understanding of attention deficit disorders, and of deficits caused by parietal lesions.

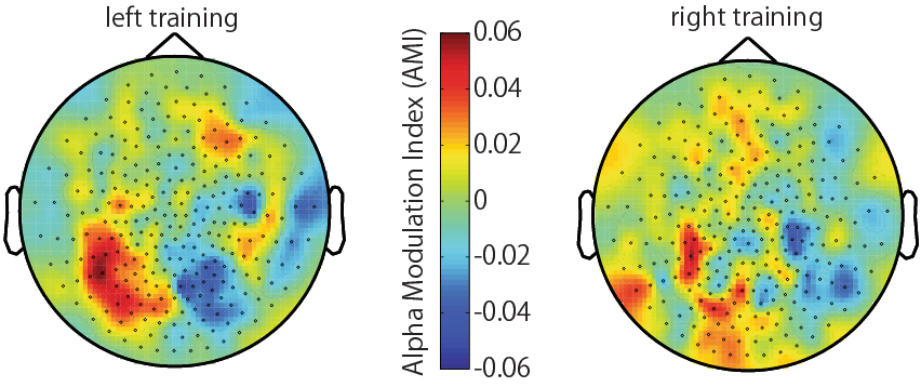
4.5 Conclusions

In conclusion, we have shown for the first time that increased alpha lateralization by neurofeedback training influences performance in a subsequent detection task. We showed that short (10 minute) real-time neurofeedback based on posterior alpha lateralization is sufficient to cause short-term behavioral changes in visual detection performance. Our study opens up the way for several future studies. In particular, we propose that future studies should aim to investigate the spatial specificity of the trained alpha lateralization and its consequence for blocking out visual distracters. Moreover, recently it has been demonstrated that ADHD patients are impaired in their ability to maintain hemispheric alpha lateralization in a spatial attention task specifically to the left hemifield (ter Huurne et al., 2013) and in their ability to suppress distraction (Adams et al., 2009; Lawrence et al., 2002; ter Huurne et al., 2013; White, 2007). As such our neurofeedback training paradigm might be suitable for treatment of ADHD patients to inhibit distracting visual input, as it reduces the detection ability of unattended visual information. This would require the long-term effects of the neurofeedback training to be assessed in longer and repeated training sessions.

4.A Appendix



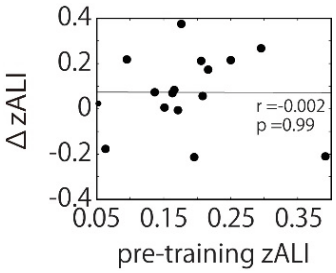
Supplementary Figure 1 The left panel shows changes in ALI over the course of the neurofeedback blocks for "learners" (ΔALI>0) and "non-learners" (ΔALI≦0), where ΔALI = last 5 blocks – first 5 blocks (**p < 0.001, error bar: STD). Only learners significantly increased the detection threshold in the untrained hemifield, i.e. the △threshold was significantly different from 0 (right panel; *p < 0.025). No effects were found for the non-learners or for the trained hemifield.



Supplementary Figure 2 Topographic plot for the left and right training group. Left panel: A clearly visible pattern of alpha lateralization in the left training group. Right panel: The right training group showed a weakly pronounced, more cluttered alpha lateralization.

Differential effects for left and right hemifield training group

The left training group shows a strong increase in alpha lateralization, while the right training group does not. We investigated possible reasons for this, and hypothesized that the initial alpha lateralization might have been different between the two groups, leading to less reliable neurofeedback and thus a weaker (i.e. absent) training effect. However, the initial alpha modulation was not significantly different between the left and the right neurofeedback training group ($t = 1.09$, $p = 0.29$). Next, we performed a correlation between the initial alpha lateralization and the change in alpha lateralization by neurofeedback training. However, we found no correlation between initial strength of ALI and training effect ($r=0$, $p=0.99$; see Supplementary Figure 3). Also, when performing the correlation separately for the left and right neurofeedback group, we were not able to find a significant relation between the initial alpha lateralization and the change due to neurofeedback training (left training: $r=-0.62$, $p=0.1$, right training $r=0.53$, $p=0.18$). Thus, by closer inspection of our data, we conclude that the difference in the training effects between the left and the right neurofeedback groups was not determined by the initial strength of alpha lateralization.



Supplementary Figure 3 Correlation analysis between alpha lateralization of the pre-training phase and the change in alpha lateralization due to neurofeedback training. There is no significant correlation between the two variables ($r=0$, $p>0.99$).

Chapter 5

Hypothesis-driven methods to augment human cognition by optimizing cortical oscillations

This chapter is based on

Horschig, J.M., Zumer, J.M., Bahramisharif, A. (2014). Hypothesis-driven methods to augment human cognition by optimizing cortical oscillations, Frontiers in Systems Neuroscience 8, 119. doi:10.3389/fnsys.2014.00119

Abstract

Cortical oscillations have been shown to represent fundamental functions of a working brain, e.g. communication, stimulus binding, error monitoring, and inhibition, and are directly linked to behavior. Recent studies intervening with these oscillations have demonstrated effective modulation of both the oscillations and behavior. In this review, we collect evidence in favor of how hypothesis-driven methods can be used to augment cognition by optimizing cortical oscillations. We elaborate their potential usefulness for three target groups: healthy elderly, patients with attention deficit /hyperactivity disorder, and healthy young adults. We discuss the relevance of neuronal oscillations in each group and show how each of them can benefit from the manipulation of functionally related oscillations. Further, we describe methods for manipulation of neuronal oscillations including direct brain stimulation as well as indirect task alterations. We also discuss practical considerations about the proposed techniques. In conclusion, we propose that insights from neuroscience should guide techniques to augment human cognition, which in turn can provide a better understanding of how the human brain works.

5.1 Introduction

Recent advances in cognitive neuroscience have provided insight into the functional mechanisms of the human brain. Neuroscientists have identified specific brain patterns, for example neuronal oscillations, that co-fluctuate with the task and behavioral performance (Buzsáki, 2006). These fluctuations are not random but depend on the specific task and cognitive settings; these findings have allowed functional hypotheses to be formed, directly tested, and confirmed. Throughout the previous decades, huge progress has been made in understanding how the human brain works, and in understanding differences across age groups, pathologies, and individuals. Applying this in-depth knowledge in practice might therefore be a key to creating brain tools for different target groups to improve different aspects of human cognition.

Cognitive functioning declines with age (Deary et al., 2009) and does not necessarily occur in the presence of a neurological disorder. Healthy elderly suffer from problems with memory and attention more than healthy, young individuals. With an increasing aging population, it has become a societal priority to look into approaches that can delay or prevent functional degeneracy or even augment cognitive abilities in the elderly. Brain tools might have the potential to rejuvenate the functionality of an aging brain.

Many people suffer from cognitive deficiencies in daily activities, but there are population groups in which these problems are more severe. Attention deficit/hyperactivity disorder (ADHD) is a well-studied disorder with problems of attention, hyperactivity, and impulsivity. Although the cause of ADHD is unknown, there have been many attempts to treat it using medication (e.g., Chang et al., 2012). Next to many unknown side-effects of medication, about 30% of the ADHD population do not respond to any medication, which calls for alternative treatments (Kidd, 2000). Brain tools might serve this population by normalizing their brain activities.

Most of our knowledge from cognitive neuroscience about the human brain stems from studies on healthy, young individuals, which have helped to form functional hypotheses about traits of human brain activity. These hypotheses can serve as a benchmark for other populations groups. In addition, also healthy young adults show large task variability in cognitive tasks. Next to individual differences, individuals' performance varies momentarily in cognitive tasks (Kane and Engle, 2002; Paulus et al., 2009). Thus, while constituting a proper control group, we will also discuss our

current knowledge on whether young, healthy adults can benefit from cognitive improvements.

The brain is a highly flexible organ which can adapt to different manipulations very quickly (Pascual-Leone et al., 2011). Brain training to augment human behavior has already been proposed in the past (see e.g. Calderone et al., 2014; Enriquez-Geppert et al., 2014; Herrmann et al., 2013; Thut et al., 2011a). We complement these reviews by proposing different techniques in different target groups to relate the to-be-augmented aspect of cognition to associated neuronal signatures, specifically neuronal oscillations. Identifying the neural signatures of different tasks will allow for proposing protocols for manipulating the brain and thereby the individual's cognitive abilities. Recent studies suggest a causal role of neuronal oscillations in cognitive tasks (Romei et al., 2010; Thut and Miniussi, 2009). Based on this hypothesis and the possibility of manipulating neuronal oscillations in several ways, we propose that by using "hypothesis-driven" approaches, one can augment human cognition by optimizing cortical oscillations. In this paper, we begin with discussing the functional role of neuronal oscillations and their cognitive relevance. We then continue with more details about three target population groups, healthy elderly, patients with ADHD, and healthy young adults, and elaborate on how cognitive improvement can be gained. Next, we go into different ways of manipulating functional oscillations in order to improve cognitive performance in the three target groups. The paper ends with practical considerations and conclusions.

5.2 Functional role of neuronal oscillations

Spontaneous and goal-related fluctuations of the brain state are reflected in electrophysiological activity that can be measured non-invasively using various techniques like electroencephalography (EEG) and magnetoencephalography (MEG). EEG and MEG measure the strength of the voltage potentials and magnetic fields at the scalp associated with postsynaptic potentials along the dendrites of pyramidal neurons, i.e., the synaptic input to these cells (Lopes da Silva, 2013; Niedermeyer and Lopes da Silva, 2005; Nunez, 2000; Wang, 2010). Non-invasive measurements require strongly synchronized activity across nearby neurons to result in a measurable signal at scalp level. Neuronal oscillations at the scalp level are rhythmic patterns that represent the degree of synchronized neuronal input to the underlying neuronal ensemble (Buzsáki and Draguhn, 2004; Lopes da Silva, 1991), which are reflected as power increases (commonly known as event-related synchronization, ERS) or power decreases

(event-related desynchronization, ERD; see Pfurtscheller and Lopes da Silva, 1999).

Neuronal oscillations are commonly divided into different frequency bands. While lower frequencies are often associated with long-range connectivity between cortical regions (von Stein and Sarnthein, 2000), higher frequencies reflect the local firing pattern of neurons (Xing et al., 2012). Furthermore, different neuronal oscillations have been associated with specific neuronal processes (e.g. Kopell et al., 2010; Engel et al., 2001), which have been related to behavioral performance, e.g., in attention and working memory tasks (reviewed in more detail below). In this paper, we will focus on cortical oscillations in three frequency bands: alpha oscillations (8-13 Hz), theta oscillations (5-8 Hz), and gamma oscillations (>30 Hz). In the following, we will introduce these three oscillations, describe the current dominant views on their function, and elucidate their role on qualitative aspects of cognition[3].

Alpha oscillations (8-13 Hz): Functional inhibition of neuronal regions

Human alpha oscillations are the dominant rhythms in EEG and MEG. They were observed almost a century ago (Adrian and Matthews, 1934; Berger, 1929) and, while originally having been associated with the idle state of the visual cortex, the current dominant view has changed towards a functional, inhibitory role, elaborated upon below. Alpha is generated via thalamocortical and cortico-cortical loops (Lopes Da Silva and Storm van Leeuwen, 1977; Lopes da Silva et al., 1980; Suffczynski et al., 2001; Bollimunta et al., 2011). Cortical alpha has been shown to be modulated by the pulvinar nucleus of the thalamus (Saalmann et al., 2012) as well as by frontal regions (Capotosto et al., 2009). The precise mediation of cortical alpha via the interplay between frontocortical and subcortical mechanisms still requires further investigation. Individual variations of alpha power appear as stable traits. The peak frequency of alpha oscillations has been related to the latent factors of general cognitive abilities, and the frequency and power of alpha oscillations have been shown to change with age (Grandy et al., 2013; Klimesch, 1999).

[3] Note that we focus on power of the oscillation and do not cover its phasic role. Other frequency bands, such as delta (1-3 Hz) or beta (13-30Hz) oscillations, or slow cortical potentials lie outside the scope of this chapter. Some alternative approaches are shortly discussed in section 5.4.

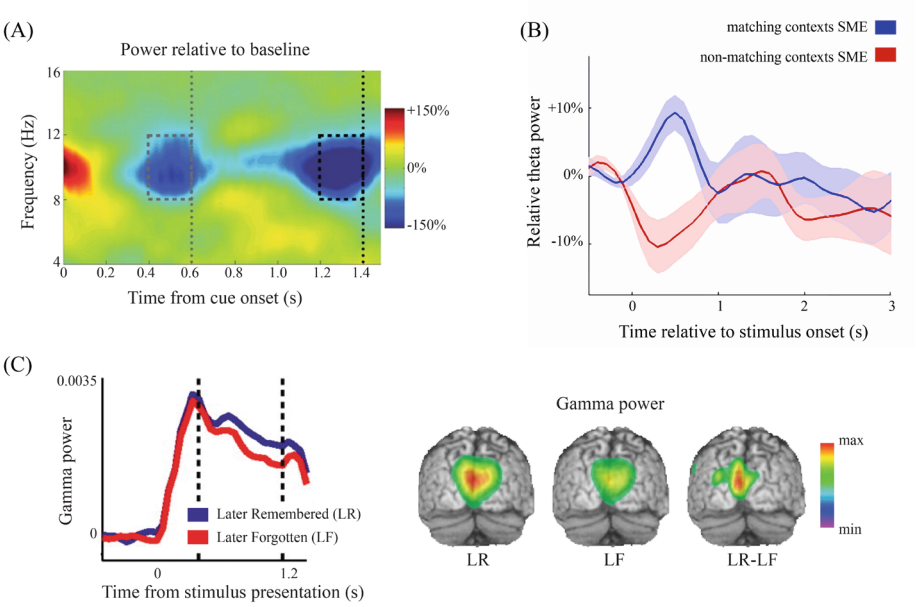


Figure 1 Example of the functional involvement of neuronal oscillations. A The time-frequency representation of an anticipation task. The grey dotted line shows the time that the stimulus could have been presented, but was not. The black dotted line indicates the onset of the target. Alpha power decreases in anticipation of a stimulus even without subsequent stimulation. Reproduced with permission from Rohenkohl and Nobre (2011). B The dynamics of frontal theta power. Depending on the encoding task, both increases and decreases of frontal theta power were found for successful versus unsuccessful remembering. SME = subsequent memory effect. Reproduced with permission from Hanslmayr and Staudigl (2014). C During visual stimulus encoding, posterior gamma power (60-90 Hz) is predictive of subsequent memory performance in young, healthy adults. The vertical dashed bars indicate the window for significance testing and beamformer application. The left panel shows gamma power from one significant posterior sensor and the right panel is the beamformer projection. Reproduced with permission from Osipova et al., (2006).

Alpha oscillations are strongly involved in attention processes. While low alpha activity can be observed in regions that are processing information, sensory regions that are not involved in the current task show high alpha activity. For example, in covert spatial attention studies, selective attention and successful inhibition of the task-irrelevant hemifield are often indexed using the extent of alpha power lateralization. Highly lateralized alpha activity thereby suggests a high inhibition of the task-irrelevant hemifield and has been shown to lead to better task performance (Kelly et al., 2009; Thut et al., 2006; Worden et al., 2000), whereas a weak or reverse alpha lateralization leads to failures in motor inhibition (Bengson et al., 2012). During the retention interval of working memory tasks, it has been shown that the degree of alpha power increase in early sensory regions scales with

memory load (Jensen et al., 2002). This effect also holds true for paradigms in non-visual domains, e.g., occipital alpha increases during a somatosensory delayed-match-to-sample task (Haegens et al., 2010; Spitzer and Blankenburg, 2012). Additionally, strong alpha during the immediate rehearsal of an item for long-term memory encoding has been shown to predict the long-term memory encoding success (Meeuwissen et al., 2011). Alpha activity has therefore been suggested to reflect the amount of top-down controlled cortical inhibition (reviewed in Foxe and Snyder, 2011; Jensen et al., 2012; Jensen and Mazaheri, 2010; Klimesch, 1999; Klimesch et al., 2007; Klimesch, 2012).

Alpha oscillations are also strongly involved in the anticipation of upcoming stimuli, which has been convincingly shown by Rohenkohl and Nobre (2011). They showed that when stimulation was temporally anticipated but absent, alpha power decreased to a similar degree compared to when stimulation actually occurred when anticipated, see Figure 1A. Moreover, the degree of anticipatory alpha power correlates with subsequent behavioral performance in attention tasks (Kelly et al., 2009; Thut et al., 2006; Worden et al., 2000) and correlates with subsequent long-term memory performance (Park et al., 2014). Anticipatory alpha power also scales with stimulation likelihood (Gould et al., 2011; Haegens et al., 2012; see **Chapter 2**). Upon stimulation, however, alpha oscillations robustly decrease in early sensory regions. Recently, Hanslmayr et al. (2012) suggested an entropy-based explanation for this: the more complex the information is that needs to be encoded, the less structured (i.e. the more de-synchronized) the activity in a network has to be. An alternative explanation, which is not mutually exclusive, is that early sensory regions become dis-inhibited, i.e. functionally engaged, and therefore show low alpha power.

Theta oscillations (5-8 Hz): Working memory and neuronal organization

Depending on where in the brain theta oscillations are observed, they can be divided into two groups of hippocampal and cortical theta rhythms (reviewed in Mitchell et al., 2008). In this paper we only focus on the cortical theta rhythms that can be measured non-invasively and are probably generated in hippocampal-cortical feedback loops (Klimesch, 1999). Cortical theta power has been related to encoding, retaining, and retrieving items in working memory (Kahana et al., 2001; Klimesch et al., 2010; Sauseng et al., 2010). The frequency of theta rhythms shows a large inter-individual variability similar to alpha oscillations, and the individual theta peak frequency has been shown to be significantly correlated to the individual alpha peak frequency (Klimesch et al., 1996).

During working memory tasks, theta power increases over temporal sites during encoding, maintenance, and retrieval (Fell et al., 2011; Raghavachari et al., 2001). Over frontal regions, theta power increases proportionally with task demands (Gevins et al., 1997). In working memory tasks, for example, a higher memory load produces stronger frontal theta activity (Jensen and Tesche, 2002). However, both frontal theta increases and decreases have been found to be beneficial for successful memory retrieval (Staudigl and Hanslmayr, 2013; see Figure 1B). Hanslmayr and Staudigl (2014) recently suggested that the context of the memory and the probe items is the crucial factor for whether theta increases or decreases upon successful retrieval. Raghavachari et al. (2006), however, argued for local theta generators where frontal theta exerts executive control and parietal theta serves to maintain items in working memory.

Apart from their role in working memory, frontal theta oscillations link prediction errors to behavioral adaptations (Cavanagh et al., 2010). Theta oscillations are also involved in long-range neuronal communication between cortical and subcortical regions including the hippocampus (Mitchell et al., 2008) and nucleus accumbens (Cohen et al., 2012, 2009) as well as for corticocortical communication (reviewed in von Stein and Sarnthein, 2000). In conclusion, contemporary theory posits that theta oscillations are crucially involved in the organization and coordination of information and for memory storage and retrieval (Buzsáki and Draguhn, 2004; Jensen and Lisman, 1996; Lisman, 2010, 2005; Lisman and Jensen, 2013; Sauseng et al., 2010).

Gamma (>30 Hz): Perceptual and multisensory binding and memory maintenance

Gamma oscillations are defined as frequencies above 30 Hz, subdivided into the lower gamma range (30-80 Hz) and the higher gamma range (>80 Hz; Ray and Maunsell, 2011; Buzsáki and Draguhn, 2004). Gamma oscillations have been implicated with active processing of information and thus increase with stimulation intensity and amount of attention to stimulation (Engel et al., 2001; Engel and Singer, 2001; Fries et al., 2001; Jensen et al., 2007). A large inter-individual variability in the gamma peak frequency has been demonstrated (van Pelt et al., 2012) as well as a correspondence between the gamma peak frequency and the characteristics of the visual stimuli (van Pelt and Fries, 2013).

Gamma oscillations are also observed during working memory maintenance (Jokisch and Jensen, 2007; Miltner et al., 1999; Tallon-Baudry et al., 1998), possibly reflecting active processing and binding of the to-be-

maintained information in frontal and parietal cortices (Polanía et al., 2012b). The degree of gamma power during encoding of visual items has been found to correlate with working memory load (Howard et al., 2003) and predicts successful memory encoding, see Figure 1C (Osipova et al., 2006). Also, during successful multisensory integration, an increase of gamma band power has been observed (Kanayama et al., 2012; Schneider et al., 2008), strengthening the idea that gamma band oscillations serve to form a coherent object representation in working memory. Gamma band activity has been suggested to reflect the process of mentally forming and binding objects (Tallon-Baudry and Bertrand, 1999; Tallon-Baudry et al., 1996).

Many studies report a simultaneous decrease of alpha power and increase in gamma power in task relevant brain regions, whereas a number of studies have shown that alpha and gamma power are not always inversely coupled (Haegens et al., 2010; Scheeringa et al., 2011). For example, while alpha power has been shown to decrease in anticipation of a stimulus (Rohenkohl and Nobre, 2011; see Figure 1A), gamma activity is induced by stimulation and active maintenance but is not observable in anticipation to stimulation (Hoogenboom et al., 2006). Thus, while alpha decreases may serve to disinhibit a brain region, gamma oscillations reflect the active, ongoing processing and binding of information.

5.3 Population target groups and their neuronal signatures

Many common individual differences in cognition can be traced back to differences in memory or attention processes. In the previous section we outlined the functional role of neuronal oscillations in cognition and presented strong evidence for a relationship between oscillatory power and behavioral performance in specific tasks. In this section, we will outline how optimizing neuronal oscillations might improve cognition in three target groups: the elderly, who commonly have problems with attention and working memory, patients suffering from attention deficit/hyperactivity disorder, and also healthy, young adults who show remarkable inter-individual differences in cognitive tasks. We will propose that optimizing neuronal oscillations might help to alleviate symptoms and improve cognition.

The elderly and their problems with attention and working memory

In the western world, there is a continuous demographic change with an increased percentage of elderly people in the population (Cohen, 2005; Peters et al., 2010). Several studies have statistically assessed the areas of compromised cognition in the elderly. Elderly people have more trouble in task switching paradigms compared to younger adults (Kray and Lindenberger, 2000). The elderly show lower performance in working memory tasks (Salthouse et al., 1991) and have reduced working memory capacity (at least in part) due to problems in binding multiple low-level features (Brockmole and Logie, 2013). Additionally, it has been shown that elderly have trouble inhibiting distracting information in unimodal tasks (Andrés et al., 2006; Fabiani et al., 2006; Folk and Lincourt, 1996; Gaeta et al., 2001; Groth and Allen, 2000; Rowe et al., 2006; Tales et al., 2002; Yang and Hasher, 2007), in cross-modal tasks (Alain and Woods, 1999; Hugenschmidt et al., 2009b; Poliakoff et al., 2006), and multi-modal tasks (Hugenschmidt et al., 2009a). The studies by Hugenschmidt et al. and others suggest that while elderly have trouble ignoring task-irrelevant items, they do show intact attention abilities. For example, elderly showed behavioral cueing effects, even in more complex environments (Hugenschmidt et al., 2009b; Hugenschmidt et al., 2009a).

In addition, a number of structural and functional changes have been reported in the brain of the elderly. For example, with increasing age, alpha peak frequency and power decrease while theta power increases (Dustman et al., 1993; Grandy et al., 2013) and the amount of evoked gamma band activity is reduced in the elderly compared to young adults (Werkle-Bergner et al., 2009). Recently, Sander et al. (2012a) proposed to disassemble working memory into two components: a global top-down control mechanism and a local perceptual binding mechanism. They further hypothesized that both components are differentially impaired in the elderly. By incorporating the reviewed evidence from the previous section, global top-down control is reflected by the power of frontal theta and posterior alpha oscillations (reviewed in Foxe and Snyder, 2011; Jensen et al., 2012; Jensen and Mazaheri, 2010; Klimesch, 1999; Klimesch et al., 2007; Klimesch, 2012), whereas local binding is reflected by gamma band oscillations (Tallon-Baudry and Bertrand, 1999; Tallon-Baudry et al., 1996). Under this framework, reduced alpha or theta power would suggest a problem with top down control, whereas a reduction in evoked gamma-power would predict a problem with perceptual binding.

A number of studies showed the absence of correlations between behavior and oscillatory activity in the elderly, while present in healthy young

adults. For example, a strong increase in frontal theta power with working memory load has been reported in young adults (Jensen and Tesche, 2002), but there was no such relation in the elderly (McEvoy et al., 2001). Also, McEvoy et al. (2001) found that with increasing task difficulty, alpha power in both parietal and frontal cortices decreased in the elderly, whereas in young adults alpha power only decreased over parietal regions. In a similar vein, Gazzaley et al. (2008) showed that frontal theta power scaled with the relevance of the to-be-processed item in young healthy adults, but not in the elderly, see Figure 2A. Sander et al. (2012b) showed that in a visual covert attention working memory paradigm, the degree of lateralized alpha power was maximal under high memory load in healthy, young adults, whereas it peaked under medium memory load in the elderly and was nearly absent in the high memory load condition. Despite the absence of this correlation, the elderly were still able to successfully perform well in this task, although worse than the young adults.

All studies in elderly are fraught with the problem that compensatory mechanisms seem to be active (Cabeza et al., 2002; Logan et al., 2002; Nielson et al., 2002; Reuter-Lorenz et al., 2000; Riis et al., 2008). While a reduced amount of activity might highlight the locus of the problem, an increase in activity elsewhere might indicate the compensation. Hence, in the above finding by Sander et al. (2012b) it is likely that a compensatory mechanism took over the functional role of posterior alpha lateralization under high memory load. Identifying such mechanisms and studying whether they are compensatory or competing with normal functioning could help in determining whether this mechanism is causing or resulting in the degraded bottom up sensory processing and binding.

Attention Deficit/Hyperactivity Disorder

Attention deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder in the western world (Barry et al., 2003; Cantwell, 1996) with an estimated prevalence of 3-6% (Pelham Jr et al., 1992; Polanczyk et al., 2007). Diagnosis of ADHD is characterized by two components: an attention and a hyperactivity component. While some patients show traits of both components (the "combined" subtype), a large proportion of patients show only one component strongly with the other component weaker or absent (Barkley et al., 1990; Lockwood et al., 2001). Here, we will focus on the combined and the inattentive subgroups, i.e., those with attention deficits. However, the combined patient subgroup is characterized by different attention deficits in cognitive tasks than the inattentive subgroup (Adams et al., 2008; Booth et al., 2007; Weiss et al., 2003), leading to the proposition of categorizing patients showing inattentive without hyperactivity symptoms

as a patient group distinct from ADHD (Barkley, 2001; Derefinko et al., 2008; Milich et al., 2001). Nonetheless, we will discuss characteristics and possible treatments for attention deficits of both the combined and the inattentive subgroups.

The inattentive subtype is characterized, as the name implies, by problems in engaging and sustaining attention. In behavioral paradigms it has been found that the inattentive subgroup showed either reduced attention resources (Carr et al., 2010) or reduced visual processing power (Weiler et al., 2002). The inattentive subtype also showed a lack of response cueing effect (Derefinko et al., 2008; Lockwood et al., 2001). Behavioral deficits and oscillatory power differences between ADHD patients and control subjects have been investigated recently. In adolescents, Mazaheri et al. (2013) found that ADHD patients of the inattentive subgroup showed a reduced behavioral cueing effect and weaker suppression of posterior alpha in response to the cue that indicates with which hand to respond. In young adults with the inattentive subtype, ter Huurne et al. (2013) showed an absence of maintaining posterior anticipatory alpha lateralization in response to a left attention cue, but not to a right attention cue. Interestingly, they found the same initial level of alpha lateralization in control and ADHD groups. In both studies, the degree of alpha power modulation with task showed a strong correlation with behavior for the control group but not for the ADHD group; see Figure 2B. These studies suggest that inattentive ADHD patients do not only suffer from reduced but also from inefficient integration of posterior alpha power as it does not seem to be beneficial for behavior, whereas it is for healthy people.

Studies on the combined ADHD subgroup and neuronal oscillations in task settings are sparse. Recently Karch et al. (2012) found that young adults suffering from ADHD showed increased frontocentral gamma band activity shortly after auditory stimulation followed by a voluntary motor response. Yordanova et al. (2001) found that ADHD children between 9 and 12 years of age showed increased induced fronto-central gamma band responses for right auditory stimulation compared to normally developing children, but not for left auditory stimulation. Lenz et al. (2008) found that children of the combined ADHD group showed enhanced visual stimulus-induced gamma power. While gamma power correlated with long-term memory performance for typically developing children, it did not for the ADHD children. In addition, Mazaheri et al. (2013) tested children of the inattentive subgroup and the combined subgroup and compared these two groups with typically developing children. They found significantly more alpha power to response cues for the inattentive subtypes compared to typically developing children (discussed above), but there was no such effect for the

combined group. The combined group, however, showed no significant difference in alpha power from the inattentive subgroup. Also, the combined subgroup showed no correlation between behavior and anticipatory alpha, whereas the typically developing children did. In an earlier study, Mazaheri et al. (2010) investigated the response preparation ability in a perceptual switching task in typically developing children compared to children classified in the combined ADHD group in age range from 8 to 12 years. Typically developing children showed a strong alpha power increase in parieto-occipital cortex in preparation for auditory versus visual stimulation, in line with the idea of shutting down the visual stream when preparing for auditory input. ADHD children, however, showed no such difference, but a frontal theta increase instead. Additionally, although in typically developing children parieto-occipital alpha power was inversely correlated with the behavioral cueing effect in the visual condition, there was no such correlation for the ADHD children. Recently, Lenartowicz et al. (2014) investigated the neuronal patterns in a group of children between 7 and 14 years of age comprised of both the inattentive and combined subgroups. In a working memory paradigm, they found reduced vigilance attributed to a less pronounced alpha depression during encoding (i.e. higher occipital alpha activity) in ADHD children than in typically developing children, but in return a stronger alpha power synchronization during stimulus maintenance in ADHD children. Frontal theta during the maintenance period was also elevated in ADHD children, which they interpreted as a compensation for the lack of vigilance during encoding.

The above studies indicate a versatile interplay of hyper- and hypo-activity in specific phases during a task. In line with Lenartowicz et al. (2014) we propose that this might be anchored to improper preparation for the task, indicated by a lack of modulating anticipatory alpha activity to stimulation. Higher gamma during stimulation and higher alpha and theta during stimulus maintenance might thus be the product of compensation for this improper preparation.

Cognition in healthy, young adults

Within young healthy adults there is a large spread of inter- and intra-individual differences in both neuronal oscillations and behavior. For example, healthy individuals differ in visual working memory capacity (Luck and Vogel, 2013). Individuals with better working memory capacity have greater frontal theta power during stimulus encoding (Gevins and Smith, 2000). Similarly, individuals with greater pre-stimulus frontal theta power better remembered source context (Addante et al., 2011). Also within subjects, high frontal pre-stimulus theta power was predictive of whether an

item was remembered (Addante et al. 2011), as was increased gamma power during stimulus encoding; see Figure 1C (Osipova et al., 2006).

The ability to sustain attention varies among individuals. Individual differences in the degree of alpha lateralization have been linked to differential abilities to ignore the task-irrelevant hemifield (Fu et al., 2001; Haegens et al., 2011a; see **Chapter 2**) as well as to working memory performance (Sauseng et al., 2009). Gamma power has been linked to improved attention as well. Apart from the fact that gamma power is commonly increased for attended versus unattended stimuli (Bauer et al., 2006; Tallon-Baudry et al., 2005), individuals with stronger gamma activity have been associated with improved perceptual processing (Fründ et al., 2007; Jokeit and Makeig, 1994). Moreover, the ratio between theta and gamma peak frequency has been successfully linked to short-term memory capacity (Jensen and Lisman, 1998, 1996), which both consistently vary from individual to individual (Kamiński et al., 2011). In future studies, explicit perturbation of the specific neuronal oscillations is required to identify whether they are causally involved in cognition and, if so, the findings can serve to form strong hypotheses on how to augment human cognition.

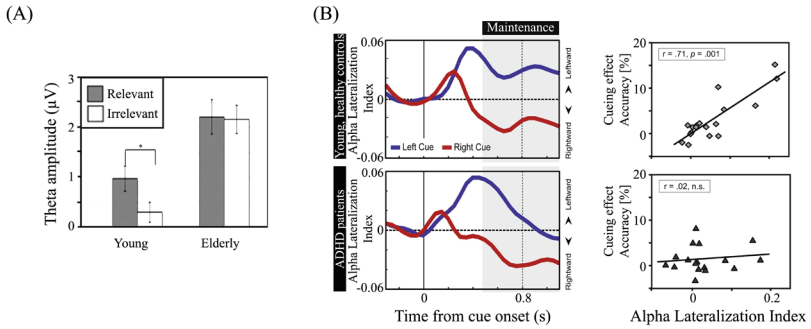


Figure 2 Oscillatory power differences in different task settings in the three discussed population groups. A Frontal theta power during stimulus encoding is significantly higher for elderly versus young adults, and scales with relevance of the stimuli in young, healthy adults, but not in the elderly (*p<0.001). Reproduced with permission from Gazzaley et al. (2008). B During visual spatial covert attention, the degree of alpha lateralization indexes the relative disengagement of the task-irrelevant ipsilateral hemisphere versus the task-relevant contralateral hemisphere. While young, healthy adults are able to modulate their alpha lateralization symmetrically around zero, inattentive ADHD patients show a lack of maintaining a high degree of alpha lateralization to the left side. In addition, there is an absence of correlation between alpha lateralization index and behavioral cueing effect in ADHD patients, whereas there is a strong relationship in healthy, young adults. Reproduced with permission from ter Huurne et al. (2013).

5.4 Techniques to manipulate neuronal oscillations

In this section we will discuss how to apply our framework in practice. We will combine the fundamental insights of neuronal oscillations from the second section with the studies on different population groups discussed in the third section to answer which oscillatory components might be suitable for optimization and whether and how this optimization could increase cognitive performance. Since there are oscillations-behavior correlations in healthy adults and oscillations-pathology correlations, optimization of neuronal oscillations could lead to optimized behavior. We will introduce different, non-invasive approaches to manipulate neuronal oscillations, outline how these techniques work, and present studies on what has already been achieved. In addition we will suggest steps to fill the gap in current literature on successful augmentation of human cognition.

Transcranial stimulation of the human brain

The most direct way to manipulate neuronal firing is by electrical stimulation to manipulate the neuron's membrane potential causing it to de- or hyperpolarize. The two common non-physically-invasive techniques to do so are transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS). TMS utilizes the fact that a changing current in a wire induces a changing external magnetic field that, if in the presence of a conducting material such as neural tissue, induces a secondary electric current in the opposite direction (Pascual-Leone et al., 1999). This secondary current then affects local membrane potentials. Although the exact mechanism is still not completely understood, it is assumed that TMS pulses primarily influence the axons of both excitatory and inhibitory neurons and might actively elicit action potentials (Dayan et al., 2013). Two basic TMS approaches are commonly used. The "online" approach applies single, double, or brief bursts of pulses, each lasting a few hundred microseconds, during the task. The "offline" approach applies repetitive stimulation (rTMS) before a task or other measurement (Huang et al., 2005). Depending on the exact pattern and frequency of rTMS, cortical excitability can be facilitated or inhibited for a period outlasting the stimulation itself from 15 up to 90 minutes (Thut and Pascual-Leone, 2010). However, it has also been suggested that the frequency of stimulation entrains the neuronal oscillations at the stimulation frequency, which outlasts stimulation for a short period of time (hundreds of milliseconds; Thut and Miniussi, 2009). There is some first direct evidence for rhythmically entraining alpha oscillations in the visual cortex by means of brief bursts of rTMS around 10Hz (Thut et

al., 2011b and Figure 3A), yet stimulation not necessarily in the alpha frequency range can induce an alpha power increase (Thut and Pascual-Leone, 2010). Several studies have provided convincing indirect evidence for rTMS entrainment by its impact on behavior (Romei et al., 2010 and Figure 3B**;** Klimesch et al., 2003; Sauseng et al., 2009a).

The basic principle of tCS is that a weak electrical current is established between an anode and cathode, thereby altering neural membrane potentials. Importantly, because of the weak electrical current, tCS cannot trigger action potentials but rather slightly facilitates or inhibits spontaneous neuronal firing, depending on its polarity (Dayan et al., 2013; Reato et al., 2013). Transcranial current stimulation can be applied in two different ways: transcranial alternating current stimulation (tACS) and transcranial direct current stimulation (tDCS). While with tDCS the polarity between anode and cathode stays constant (see Priori (2003), for a review), with tACS the polarity constantly changes, thereby producing an alternating flow of current similar to an oscillation (Antal and Paulus, 2013; Herrmann et al., 2013; Reato et al., 2013). Sometimes tACS is used in conjunction with a DC offset. In that case, the polarity between anode and cathode stays fixed, as the current strength oscillates around the DC offset instead of zero. Consequently current only flows in one direction, from the cathode to the anode, which is in contrast to the classical tACS definition, where not only current strength but also direction changes throughout each oscillatory cycle. Here, we will explicitly clarify if we refer to tACS studies with a DC offset.

In the past a number of studies has shown improved cognition or performance in tasks using tCS or TMS (Snowball et al., 2013; Meinzer et al., 2013, 2012; Vollmann et al., 2013; Schutter; Coffman et al., 2014; Luber and Lisanby, 2014). However, most of these studies did not use tCS or tACS to stimulate neuronal oscillations or concurrently recorded them by EEG or MEG. In the following we will summarize a number of studies that used tACS or TMS to stimulate in the alpha, theta, or gamma range.

Although this is a relatively recent field, a number of studies have demonstrated that stimulating in the alpha range results in sustained alpha power increases in the cortex. Zaehle et al. (2010) showed that applying tACS offline for ten minutes at the subject's individual peak alpha frequency over left and right posterior cortex resulted in an increase in alpha power for at least 3 minutes after the stimulation. Neuling et al. (2012) used tACS with a DC offset to entrain a 10 Hz rhythm during the task. After 3 blocks of 7 minute stimulation, alpha power increased post-stimulation during a measurement lasting 3 minutes. In a more recent study, Neuling et al. (2013)

found that the increase in alpha power using tACS without a DC offset lasts for up to 30 minutes. However, neither of these two studies found an influence of the power increase on behavior.

In contrast, several studies have found effects of entrainment in the alpha band on behavior using TMS, albeit they do not *per se* show that they were successful in changing cortical alpha power. Hamidi et al. (2009) applied rTMS at 10 Hz in parieto-central regions during the 3 second maintenance period in a delayed-match-to-sample task and found beneficial effects for a spatial working memory task, but not for a non-spatial working memory task. This is in line with the idea that high alpha power is needed during working memory maintenance to block additional incoming information and that the dorsal (parietal) regions encode spatial information but inferior (temporal) regions encode identity information (Goodale and Milner, 1992). Interestingly however, while Hamidi et al. (2009) did not find a change in alpha power due to TMS at the group level, they did find an across-subjects correlation of alpha power with behavior. Romei et al. (2010) found that entraining the alpha rhythm ipsilateral to the attended hemifield increased perceptual accuracy, whereas entraining alpha contralaterally decreased accuracy, strongly in line with the idea that strong alpha inhibits processing (Figure 3B). However, the effect of TMS stimulations on neuronal oscillations was not concurrently assessed by EEG, so it remains to be investigated whether the stimulation also resulted in changes in cortical oscillations.

Brignani et al. (2013) also tried to increase the ipsilateral alpha rhythm but with tACS to parieto-occipital cortex. Surprisingly, they found no spatially specific effect but a general task impairment during a covert spatial attention task. This might have been caused because the stimulated area using tCS is widespread and not easily inferable from the placement of the anode and cathode (Bai et al., 2014; Manoli et al., 2012). Also in this study, no concurrent EEG recordings were done, so the effect of stimulation on cortical oscillations could not be directly assessed. These studies show that different brain regions are affected differently by different techniques on different target areas and that precise *a priori* hypotheses and knowledge about the brain region to be stimulated are necessary for successful augmentation of human cognition. *A priori* computational modeling of the stimulation protocol using advanced physical models has recently been demonstrated (tCS: Bai et al., 2014; Manoli et al., 2012; TMS: Bijsterbosch et al., 2012; Janssen et al., 2013; Wagner et al., 2014). This could help in applying protocols and stimulation electrodes and thereby aid in studying whether modulation of cortical alpha power in specific regions has behavioral consequences.

Fewer studies are available which attempt to induce theta oscillations. Meiron and Lavidor (2014) applied tACS in the theta range to bilateral frontal cortex during a working memory task and found an improvement in online working memory capacity. Jaušovec and Jaušovec (2014) used tACS in the theta range but around left parietal cortex and showed that this leads to an improved memory working memory span. Jaušovec et al. (2014) replicated their finding on stimulating the theta rhythm, but this time in bilateral parietal cortices and replicated the effect on improved working memory capacity. They also report a null-effect for stimulating frontal cortex. While these findings suggest that entrainment of the theta rhythm is spatially specific and results in increasing working memory, they did not report oscillatory responses to assess whether the theta power was successfully increased over the stimulated area. In addition, none of these studies used control frequencies to show a frequency specific effect. Further studies are required to measure spatial and spectral specificity, disentangle which part of working memory is affected, and show convincingly that theta oscillations are entrained or at least modulated during stimulation.

In the gamma range, Chanes et al. (2013) showed a differential effect on performance in a perceptual detection task for 30 Hz stimulation versus 50 Hz stimulation using TMS to right frontal eye fields, where the former enhanced perceptual sensitivity and the latter shifted the response criterion. Using tACS, Santarnecchi et al. (2013) showed that entraining gamma around 40 Hz at the left mid-frontal gyrus improved performance in conditioning and reasoning tasks. Laczó et al. (2012) showed that gamma stimulation to early visual cortex around 60 Hz but not at 40 Hz or 80 Hz resulted in a lower contrast detection threshold. Importantly, none of the stimulation frequencies resulted in behavioral changes in spatial detection tasks. While showing promising results, studies on rhythmically entraining the gamma range are sparse and differ in exact frequency range and spatial location. Reproductions of these findings are required in order to draw definite conclusions on where and how to stimulate to improve what aspect of perceptual performance by gamma entrainment.

All of the above reviewed literature was on healthy, young adults and not on other target groups. Given the partly incomplete literature and understanding of TMS and tACS, it remains to be tested whether such hypothesis-driven brain stimulation shows success in the elderly and ADHD patients, and whether this results in a reduction of cognitive problems.

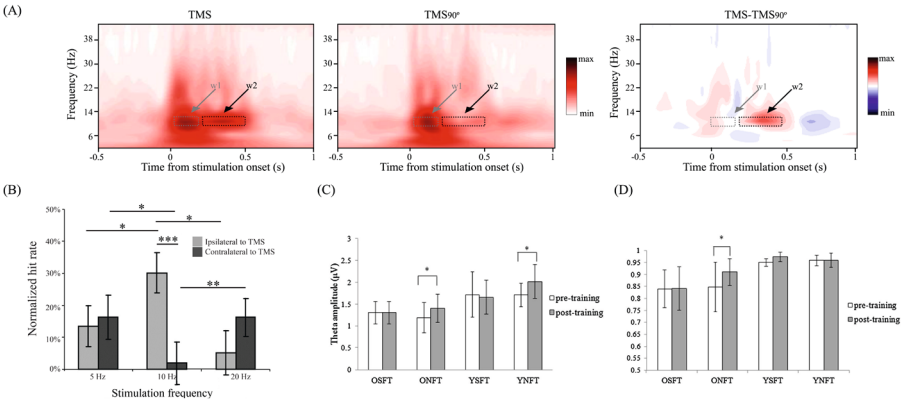


Figure 3 Examples of manipulating neuronal oscillations and their impact on cognition. A rTMS stimulation at 10 Hz to right parietal cortex results in alpha oscillations outlasting the stimulation period (t=0s), compared to the control condition of rotating the TMS coil by 90 degrees (TMS90). The condition contrast with other control conditions confirmed the exclusive effect of rTMS at 10 Hz. w1 = time window of the first two pulses and w2 = time window of the last three pulses. Reproduced with permission from Thut et al. (2011b). B 10 Hz rTMS stimulation, but not 5 Hz or 20 Hz, of parietal cortex ipsilateral to stimulation results in behavioral improvement, whereas contralateral stimulation results in decreased performance (*p<0.05, **p<0.01, ***p<0.001). Reproduced with permission from Romei et al. (2010) C Frontal theta neurofeedback training results in increased frontal theta in both young and old adults. OSFT = old subjects, sham feedback; ONFT = old subjects, neurofeedback group; YSFT = young subjects, sham feedback; YNFT = young subjects, neurofeedback (*p<0.01). Taken with permission from Wang and Hsieh (2013). D Only old adults receiving neurofeedback on frontal theta increased working memory accuracy in a Sternberg task (depicted on the y-axis). Young adults were already performing at ceiling level. (for acronyms, see Figure 3C; *p<0.01). Taken with permission from Wang and Hsieh (2013).

Hypothesis-driven brain computer interfacing and neurofeedback

Brain-computer interfacing (BCI) commonly refers to the technique to use a signal measured from the brain to control a computer or a machine without the use of the peripheral muscle system (Wolpaw et al., 2002). This requires the user's awareness of the ongoing brain activity, which is made perceivable by means of visual, tactile, or auditory feedback (van Gerven et al., 2009b). The original goal of BCI was to provide the user with an additional output channel for the purpose of communication.

Neurofeedback serves a different purpose by similar means. The goal of neurofeedback is to make the users aware of their brain activity to learn to enhance or decrease the fed back aspects, e.g., theta power, and thereby alleviate pathological symptoms, such as in ADHD (Fuchs et al., 2003; Lubar et al., 1995). An unfortunate major criticism in the field of neurofeedback, however, is often the absence of control conditions, significant

effects, a scientifically grounded hypothesis, or reproducibility (see Vollebregt et al., 2013). Recently it has been proposed to start using hypothesis-driven BCI to improve subsequent behavior (Jensen et al., 2011), on which we will now elaborate.

Hypothesis-driven BCI (hdBCI) refers to the idea that insights from fundamental and cognitive neuroscience are applied to infer a robust and reliable control signal to improve cognition. Such a control signal must show strong single trial correlation with behavior and must be trainable. As described above, neuronal oscillations have been well studied and show strong correlation with cognition in a multitude of task settings ranging from attention or working memory studies to studies on long-term memory encoding and retrieval. This robustness and reliability allows making a concrete hypothesis to be tested when applying neurofeedback techniques. We suggest using a control signal that shows strong correlations with behavior, for example frontal theta during working memory or alpha lateralization during covert visual spatial attention tasks, and trains the subjects to gain awareness and control of that signal. Before and after hdBCI training, a number of behavioral tasks orthogonal to the hdBCI task should be used to assess whether the neurofeedback training translates to subsequent improvements in cognition. The neuronal oscillation and the hdBCI paradigm need to reflect the underlying cognitive mechanism to be trained. For example, we described problems with general attention and reduced ability to suppress distracting stimuli in the elderly or in ADHD patients - a functional role that alpha oscillations are supposed to fulfill. The aim of hdBCI training is to study whether the training effect on oscillatory power brings along changes in behavior, in particular ideally, that has been shown to be correlated to that oscillation. If subsequent behavioral improvements in untrained, but related tasks are found, this would serve as a strong case that neuronal oscillations are causally involved in cognition. In the following we will review studies that can serve as templates for how hdBCI training can be used to study the functional role of neuronal oscillations.

While alpha-based neurofeedback has been shown to modulate not only the alpha power but also performance on a mental rotation task (Hanslmayr et al., 2005b; Zoefel et al., 2011), we link the findings of alpha power's role in inhibition of distracters (see **Chapter 5.2**) to hdBCI training with the goal of improving resilience to distraction. No such study has been conducted so far. If successful, one might ask whether the same rationale can be used for treating inattentive symptoms of the elderly or ADHD patients. As a concrete example, one could study whether the alpha lateralization pattern during covert spatial attention can be trained and strengthened. Alpha lateralization has been studied intensively in the past

and has been shown to be a reliable control signal for BCI (Bahramisharif et al., 2010; Kelly et al., 2005; Tonin et al., 2012; van Gerven et al., 2009a; van Gerven and Jensen, 2009). In healthy young adults, high memory load coincided with strong alpha lateralization during a covert attention working memory task - an aspect that was missing in the elderly (Myriam C Sander et al., 2012). An hdBCI can consist of training alpha lateralization in the elderly asking whether strong alpha lateralization will be of beneficial nature as observed in young adults and whether a correlation between alpha lateralization and high memory load will reemerge. In a similar line a lack of maintaining alpha lateralization has been found in inattentive ADHD patients (ter Huurne et al., 2013). HdBCI training on maintaining a high degree of alpha lateralization could help to restore this ability. Again, a correlation between behavioral performance and degree of alpha lateralization was observed in healthy adults, but lacking in ADHD patients. The most critical question is, if the ability to maintain a high degree of alpha lateralization is restored in inattentive ADHD patients, will the underlying mechanisms leading to the alpha power shifts be beneficial for their performance again? No studies in this direction have been pursued so far, but they would elucidate the functional role of alpha oscillations.

Complementarily, during working memory paradigms it has been shown that frontal theta reflects the memory load in healthy individuals (Jensen and Tesche, 2002), but no such relation was found in the elderly (McEvoy et al., 2001). One might ask whether training the elderly to increase their frontal theta proportional to memory load during a working memory task results in improved working memory performance. Recently, Enriquez-Geppert et al. (2014) and Wang and Hsieh (2013) provide preliminary evidence that frontal theta neurofeedback training does work. The latter shows that both young and old participants learned to increase frontal theta by neurofeedback in contrast to control groups (see Figure 3C and 3D). In addition elderly receiving frontal theta neurofeedback training showed improved performance in a subsequent working memory task in contrast to the control group. However, they do not show whether the neurofeedback training restored the correlation between memory load and frontal theta in the elderly. Also their study was confounded by several other issues, for example young, healthy, adults were performing at ceiling level already before the training, which resulted in a null-effect training for them. Thus, this study is inconclusive on whether frontal theta training increases working memory capacity in young, healthy adults. For ADHD patients it has been found that frontal theta is already relatively high compared to young healthy adults, e.g. during working memory encoding, which might be caused by a lack of proper preparation to the task, quanti-

fied by weaker anticipatory alpha oscillations in posterior regions (Lenartowicz et al., 2014; see also **Chapter 5.3**). Given all reviewed literature, it seems plausible that an additional increase in frontal theta during encoding or increase in posterior alpha in anticipation of the stimulus would further boost working memory performance.

Neurofeedback on gamma oscillations has been studied by Keizer et al. (2010), who found that successful increases in gamma band power in young, healthy adults correlated with an increase in fluid intelligence and reduced cost of feature binding reflected in the lower reaction times. In line with the current view on feature-binding problems in the elderly (cf. Sander et al., 2012a), Staufenbiel et al. (2014) used neurofeedback training of gamma oscillations in the elderly. Although the neurofeedback training resulted in increased gamma, they failed to show a beneficial nature of this training for fluid intelligence, working memory, and quality of life. However, these studies did not feedback gamma power during stimulation, but during resting state. It might have been beneficial to give feedback of gamma power during stimulation, as the neural sources processing stimuli are likely to differ from resting state sources, when no stimulus is being processed. No studies on training gamma band in ADHD patients have been conducted.

For a more complete overview on neurofeedback studies, the interested reader is referred to Gruzelier (2013). In general, we advise that neurofeedback studies should follow hypotheses and paradigms that are more focused and grounded in insights gained from fundamental and cognitive research conducted in the last decades, in particular using information on the functional role of neuronal oscillations.

Brain state dependent tasks (BSDT): Adapting the environment to the user's mental state

The former approach aimed at shaping the user's brain activity for optimal stimulus processing or task performance. Recent insight in the field of cognitive neuroscience (see **Chapter 5.2**) suggests that we can predict cognitive behavior by neuronal oscillations. This knowledge can be used to adapt the task environment based on the user's current brain activity to allow for optimal performance. Ultimately this could aid the user to develop an optimal brain state more quickly or efficiently. Specifically, the timing and properties of the task would be determined by an online read-out of the current brain state, as quantified by ongoing neuronal oscillatory activity (Hartmann et al., 2011; Jensen et al., 2011). It is even possible to combine this with active brain stimulation (Silvanto and Pascual-Leone,

2008), which was recently demonstrated by Gharabaghi et al. (2014), who applied TMS and provided haptic feedback according to relevant neural oscillatory activity.

Brain state dependent tasks (BSDT) serve two purposes. First, by adapting the environment to the ongoing brain activity, individual cognition could be improved as described below. Second, BSDT informs the user about his ongoing brain state and rewards the user for a "good" brain state in a similar manner as in brain-computer interfacing. BSDT therefore could help the subject's ability to modulate his brain activity to reach a certain mind setting, or brain state. BSDT can be used in two complementary manners. First, stimulus presentation can be triggered to ongoing oscillatory activity. For example, it has been found that strong prestimulus alpha power in task-relevant regions negatively affects subsequent stimulus processing (e.g. Ergenoglu et al., 2004; Hanslmayr et al., 2005a, 2007; van Dijk et al., 2008; Mazaheri et al., 2009). In a BSDT paradigm, stimulus presentation could thus be triggered only when alpha power is relatively low, thereby increasing efficiency of stimulus processing. A reverse rationale applies, where the task is to inhibit some aspect of the environment: stimulate during high alpha power in task-irrelevant brain regions. For example, background speech might be distracting when visually learning vocabularies. Thus, in a BSDT environment one could first reward high temporal alpha by removing some artificially-added, auditory distraction while visually presenting vocabularies and, in a second step, additionally only present vocabularies when posterior alpha power is low. This could lead to increased processing of the visually presented vocabularies and also increased inhibition of the distracting auditory noise. To generalize this idea, training could be provided in a variety of tasks where the direction and location of alpha modulation varies; this way, it is the control of alpha that is important and learned, not just a focal or unidirectional lesson which might interfere with other tasks. The subject thereby learns the skill to consciously modulate brain oscillations in similar manner to neurofeedback.

A second manner for BSDT is the fact that based on the activity during stimulus processing or maintenance, subsequent behavior can be predicted, as already proposed e.g. by Mazaheri et al. (2009). For example, increased alpha activity during visual processing (Park et al., 2014) and during the retention interval (Meeuwissen et al., 2011) has been shown to strongly correlate with long-term memory encoding performance. Based on these findings, one could predict which items are most likely to be forgotten and present these items again to the subject in order to facilitate long-term memory performance. In addition, measures correlating with

memory load, e.g. frontal theta or occipital gamma for visual items, can be read out to predict the current load. This could also be used to prevent memory overload (discussed in Huggins et al., 2014). This second manner represents an online adaptation of the environment and cannot necessarily be utilized offline or result in an offline skill.

For young, healthy adults, strong correlations between oscillatory power and cognition have been found as reviewed in **Chapter 5.2** and **Chapter 5.4**. However, in **Chapter 5.3** we also review evidence that this correlation seems to be absent in the elderly and ADHD patients. In these population groups, compensatory mechanisms might have taken over the function that some oscillations usually represent. While brain stimulation techniques aim to restore the beneficial nature of these oscillations, BSDT aims to predict cognition. It remains to be tested whether BSDT is beneficial for the elderly and ADHD patients when utilizing hypotheses based on another population group. Both manners of applying BSDT - waiting with stimulation until a good distribution of oscillatory power and predicting subsequent behavior by the distribution of oscillatory power - might prove useless, without a correlation between oscillation and behavior. We would therefore advise to identify neural signatures of the compensatory mechanisms, and find appropriate hypotheses for these population groups, or to manipulate the neural oscillations as proposed in the previous two subsections before applying BSDT in a patient group.

5.5 Practical considerations

In the previous section we made some concrete suggestions on how insights from cognitive neuroscience can be applied to augment human behavior. In this section, we will discuss how to define successful interventions, outline practical considerations about our hypothesis that should be regarded when following above suggestions, suggest alternative approaches, and point to possible pitfalls when applying these techniques in the lab, at home, or when valorizing these ideas for commercial use. For ethical considerations, we encourage the reader to read the Nuffield report on neurotechnology (Nuffield Councils on Bioethics, 2013).

Defining and assessing success

We have collected supporting evidence for hypothesis-driven approaches to augment human behavior. Although literature on this topic is relatively sparse, studies often differ in crucial aspects such as motivation for the study (i.e. the original hypothesis), methodology (e.g. control conditions, number or duration of training sessions, , or the number of hours or days

after training to test for long-term effects), and conclusions on how to generalize the findings. The most important question to ask when drawing conclusions about these studies is how best to quantify if the applied technique resulted in augmentation of cognition. This question can be disentangled into two parts.

First, we need to quantify that the augmentation effect is caused by the applied technique and not by confounding other reasons. For example, proper control conditions in neurofeedback settings yield results similar to neurofeedback protocols often used for ADHD treatment (van Dongen-Boomsma et al., 2013; Vollebregt et al., 2013). Thus, special care needs to be taken when attributing the beneficial effect to the applied technique, and that the effect is specific to the modulated frequency-band. As another example, it has been shown that auditory perception of the clicking sound of TMS stimulation alone is sufficient to induce an effect in visual cortex (Romei et al., 2012). Other control conditions aside from sham stimulation, such as cognitive behavioral training (Safren et al., 2010; Strenziok et al., 2014) or physical exercise (Halperin and Healey, 2011; Verret et al., 2012), are often more easily applied than brain stimulation techniques. Furthermore, it is very important to be aware of misleading causes of experimental observations, such as temporal ordering of the tasks; a randomized design order is a crucial part of any paradigm.

Second, we need to define what we mean by augmentation of cognition. We first need to define a baseline level of performance before starting the intervention and we need to show a strong, significant increase from this baseline, above the appropriate control discussed above. Additionally, an improvement in one skill might come at a cost in another skill (Brem et al., 2014; Reinhart and Woodman, 2014). Therefore, one core assertion of successful augmentation of human cognition needs to be measured by transfer learning (Dahlin et al., 2008; Klingberg, 2010; Klingberg et al., 2002), i.e. quantifying how the intervention translates to other domains that were not explicitly trained and tempered by any deficits gained in other domains. In other words, one need to clearly establish the scope of the intervention and what does and does not work.

The danger of undesired side effects

One important aspect to consider when proposing any study with stimulation is to *a priori* think about which brain region to stimulate and for what purpose. In the vast majority of this article, we talked about how to manipulate neuronal oscillations, but for successful augmentation of human cognition one needs to understand that the human brain is organized into

different cortical and subcortical structures and each serves multiple, partly overlapping functionalities. When considering augmenting human cognition, one needs to be precise on which part of human cognition. Let us take the example of increased alpha power in task-irrelevant regions. Firstly, one needs to define "task-irrelevant"; for example, in a covert visual spatial attention task, the posterior ipsilateral hemisphere is "task-irrelevant", but not the contralateral hemisphere (Kelly et al., 2009; Thut et al., 2006; Worden et al., 2000). Secondly, the natural region(s) exerting modulation of the task-irrelevant region(s) should be noted; for example, it has been found that the intraparietal sulcus and the frontal eye fields exert top-down control on posterior areas and that stimulating them has consequences for posterior alpha and subsequent behavior (Capotosto et al., 2012a, 2009; Sauseng et al., 2011). Thirdly, stimulation of the "wrong" brain region can lead to unexpected, reversed effects, i.e. where stimulation of one brain region is beneficial for one task and impedimental for another task (Iuculano and Cohen Kadosh, 2013; Romei et al., 2010); for example, when conducting a purely auditory task, the whole visual cortex becomes 'task-irrelevant'. Note that the anatomical precision of non-invasive EEG recordings is not high enough to verify the spatial specificity of the measured oscillations. While source reconstruction techniques can increase spatial certainty beyond sensor level information, invasive recordings are necessary for precise spatial localization.

Additional side effects can arise from improper task settings. For example, one might think to save time by concurrently testing for items in memory while memorizing new items. This, however, has been found to be inefficient and led to deteriorated memory performance (Huijbers et al., 2009). In addition, the functional hypothesis has to be correct and grounded in previous findings. For example, while many studies have convincingly related alpha power with inhibition of task-irrelevant regions, this might not hold true for all brain regions (Mo et al., 2011). Thus the exact experimental paradigm has to be vigorously thought through, which requires intensive knowledge from an expert in the field of cognitive neuroscience and/or brain stimulation or hdBCI techniques. Therefore, one needs to be sure which region requires which treatment (e.g. excitation is distinct from release from inhibition) in order to augment cognition successfully without burdensome side effects.

Non-optimal stimulation protocols and task settings might not be the only cause for side effects. As the mechanism behind electromagnetic brain stimulation is not fully understood, a number of unforeseen side effects can occur. Manufacturers restrict the maximum amplitude in their amplifier to a rather low value to reduce the possible risks (e.g. infrequent re-

ports of inducing seizures, kindling, mood changes and scalp burnings) which can be further minimized by following general guidelines (Rossi et al., 2009; Wassermann, 1998). In addition, effects of long-term electromagnetic brain stimulation are rarely studied and not well understood. As Antal and Paulus (2013) wrote about the motor evoked potential (MEP): "Increasing the duration of transcranial direct current stimulation (tDCS) results in a prolongation of the induced aftereffects (Nitsche and Paulus, 2000) up to about 13 min whereas doubling the 13 stimulation to 26 min inverses MEP aftereffects into inhibition (Batsikadze et al., 2013). It is unclear if this can be translated to tACS, too." While an aftereffect reversal is an obvious crucial side-effect and would be undesired, e.g. in the case of attention boosting, even stronger side effects might occur, especially due to the unknown long-term effects on plasticity and anatomical and functional connectivity. Plastic white matter changes in humans have been found following behavioral training (Sampaio-Baptista et al., 2013; Zatorre et al., 2012), and there is some preliminary evidence for white matter changes following electric stimulation (Allendorfer et al., 2012) and neurofeedback (Ghaziri et al., 2013).

Individual differences

Cognitive neuroscience aims to infer general mechanisms of the brain by studying a subgroup of some homogenous population. Significant statistical tests using random effects analysis then allow making inference from the subgroup to the population. However, finding a group level effect does not automatically mean that all individuals show the same effect, or even a significant effect. An example is found in the strength and adaptation of alpha lateralization (see e.g. Händel et al., 2011; **Chapter 2**). Interindividual variability has extensively been described as an issue in the field of brain-computer interfacing, where it has been found that about one fifth of all individuals are unable to gain control over the control signal (Dickhaus et al., 2009; Vidaurre and Blankertz, 2010). A similar kind of intersubject variability is reported in tCS techniques, which might arise due to a multitude of factors (Horvath et al., 2014; Krause and Cohen Kadosh, 2014). Thus, while we are proposing that these techniques can be used to decrease interindividual variability, it might be that interindividual variability requires different solutions for different subjects, e.g. different frequency bands or a different location of stimulation sites.

Alternative aspects of neuronal oscillations to utilize

In this review, we focused on the region-specific power of neuronal oscillations because, as discussed in **Chapter 5.2**, they are a robust read-out of the

brain state and show strong across-trials correlations with behavior. However, investigating the power of neuronal oscillations is not the only means of quantifying electrophysiological data. The alternatives we discuss below, as well as others not mentioned, may also provide a handle with which to augment cognition via manipulation as discussed in **Chapter 5.4**, if a suitable hypothesis can be formed linking neural activity to behavior. We believe however that our main point has been sufficiently illustrated by the examples (i.e. oscillatory power and patient groups) used.

One natural alternative to power is the phase. In particular, the phase of the alpha and theta oscillations has been studied intensively in the past (Buzsáki and Draguhn, 2004; Montemurro et al., 2008; VanRullen et al., 2014). Recent evidence suggests that specific phases are more optimal for specific tasks (Gho and Varela, 1988; Kruglikov and Schiff, 2003; Mathewson et al., 2009). For example, ignoring a distracter is more successful in a specific phase of alpha oscillations than in its opposed phase (Bonnefond and Jensen, 2012). Interestingly, it has also been shown that tACS can be used to gain control over the phase of an oscillation (Helfrich et al., 2014; Jaegle and Ro, 2014; Strüber et al., 2014; Zanto et al., 2014), which has corresponding, orthogonal behavioral effects. Recent studies also indicate that a visual stimulus regularly flickering at 10 Hz can entrain alpha oscillations in visual cortex outlasting the stimulation period and also that subsequent behavior was modulated in a phasic manner according to the phase of the stimulation flickering (de Graaf et al., 2013; Mathewson et al., 2012; Spaak et al., 2014). In conclusion, studying the phasic nature of oscillations will provide further insight into human perception and provide important, additional information for brain stimulation techniques, hypothesis-driven brain-computer interfaces, and brain state dependent tasks.

Furthermore another quantification of oscillations includes cross-frequency phase-amplitude coupling, whereby the phase of a slower oscillation is linked to the amplitude of a faster oscillation. For example it has been shown that gamma power waxes and wanes with the phase of alpha or theta oscillations (Bonnefond and Jensen, 2013; Canolty et al., 2006; Jensen et al., 2012; Lisman and Jensen, 2013; Roux and Uhlhaas, 2014). This also has important implications for behavior as, already discussed briefly in **Chapter 5.2**, the ratio between a theta cycle and a gamma cycle has been suggested to determine working memory capacity (Jensen and Lisman, 1998, 1996; Kamiński et al., 2011). This knowledge could be used to optimize cross-frequency coupling in order to study its direct effect on behavior.

In addition, we also chose not to focus on connectivity between brain regions, which can be a phase adjustment across regions (Fries, 2005; Gross et al., 2004; Sauseng and Klimesch, 2008; Varela et al., 2001) or a simultaneous power adjustment (e.g. Mazaheri et al., 2009). For example, several studies found a different functional connectivity pattern in the elderly compared to healthy, young adults (Geerligs et al., 2014, 2013; Hogan et al., 2011; Oh and Jagust, 2013; Onoda et al., 2012; Waring et al., 2013). In children with ADHD compared to typically developing children the pattern of functional connectivity is also different (Mazaheri et al., 2010; Murias et al., 2007). Further evidence for the importance of functional connectivity comes from TMS/tCS studies showing that not only is the activity in the stimulated region modified, but also connectivity of the stimulated region to other regions (Polanía et al., 2012a; Shafi et al., 2014; Strens et al., 2002; Veniero et al., 2013) and in some cases this altered connectivity correlated with task modulations (Vidal-Piñeiro et al., 2014) or improved/altered behavior (Lee and D'Esposito, 2012). As the human brain is a huge network of neurons, it seems logical that an optimization of functional connectivity within and across brain-regions is a crucial aspect to optimize human behavior. However, we have just begun to understand the mechanisms behind inter- and intra-regional coupling (Callaway, 2004; Canolty et al., 2006; Felleman and Essen, 1991; Fox et al., 2005; Haegens et al., 2011b; Lakatos et al., 2008; Maier et al., 2010; Schroeder and Lakatos, 2009; Spaak et al., 2012; Varela et al., 2001), so we still have a long way to go until we fully grasp the effect that artificially manipulating functional connectivity has on the human brain and human cognition.

Problems of usage at home

Applying some of these techniques at home can be a challenge on its own. The most obvious question to ask is whether the proposed techniques can be used alone at home or whether an expert, e.g. a neuroscientist or a physician with proper training, should be visited. Currently, there is a trend in crowd funding and open source projects, which allow individuals to propose and share ideas. This has led to projects such as OpenrTMSv(http://open-rtms.sourceforge.net/)-
or OpenBCI (http://www.openbci.com/), which in theory allow everyone to create their own TMS or BCI protocol. As the human brain is overly complex, however, special care has to be taken on this path of neuro-hacking (http://en.wikipedia.org/wiki/Neurohacking). Obviously side-effects, as discussed above, are likely to occur during improper application. Apart from that, additional problems can be expected when applying the discussed brain augmentation techniques at home, e.g. motivational reasons can cause irregular, inefficient use and eventually lead to stopping the

treatment. In addition, environmental noise may influence the measurements at home differently than in a well-controlled laboratory. Studies in the lab under special, controlled circumstances might not easily transfer to use at home or other situations of daily life (see e.g. Vaughan et al., 2006). Therefore and especially due to medical reasons we would propose that, first, more research is required to investigate side-effects and long-term effects. Second, application should only be administered by trained experts. Only in the far future does usage at home seem realistic.

Considerations for successful valorization and commercialization

The above suggestions and hypotheses might seem like a great promise for augmentation of human behavior, so it is natural that commercial companies will pick up on these ideas in the near future. However, when considering augmentation of human behavior from a commercial perspective, there are additional considerations apart from those already discussed, foremost safety issues. Modern advertisements focus on short, catchy messages to attract potential customers (Dahlén and Rosengren, 2005; Kohli et al., 2007). The human brain, however, is a complicated machine and we are just beginning to understand its fundamental mechanisms and functions. Companies have to take responsibility for the products they sell and be wary of linking false promises to their commercial products. Also, companies need to be explicit to the customer on the consequences of not using devices properly as intended. Yet, there is no consensus on proper use of brain stimulation technique. Thus, extreme caution needs to be exercised before bringing a product onto the market. We therefore advise any company with serious perspectives on developing and selling these devices to collaborate strongly with established neuroscientists in the field and ethical committees and to conduct extensive studies on their products.

5.6 Conclusions

In this review, we started from the hypothesis that neuronal oscillations serve as strong neuronal correlates of behavior and are involved in human cognition. We reviewed this hypothesis in light of three target groups: the healthy elderly, ADHD patients, and healthy young adults. Most of the evidence supporting our hypothesis stemmed from studies on healthy young adults showing reliable correlations between the power of the oscillations and cognitive aspects of human behavior, e.g. working memory capacity or detection accuracy. Our hypothesis was corroborated by brain stimulation studies using TMS and tACS showing a strong link between the strength of induced neuronal oscillations and behavioral performance (see **Chapter 5.4**).

This hypothesis has important implications for the realm of cognitive neuroscience: if an oscillation is causally involved in cognition, a manipulation of that oscillation has to lead to a subsequent change in behavior. Such a strong, functional hypothesis helps to drive the field of cognitive neuroscience forward in understanding how the human brain functions.

Further, we hypothesized in **Chapter 5.3** that the elderly and ADHD patients suffer from a lack of integrating neuronal oscillations properly, due to an absence of correlation with behavior, and that compensatory mechanisms could have taken over the functional shaping of cognition. We further hypothesized that manipulating neuronal oscillations in these target groups might restore their beneficial nature. This is a far-fetched claim without any empirical evidence and should be further studied. First of all, we need to ask whether the absence of the correlation between neuronal oscillations and behavior still allows the control and modulation of oscillations. Further, if these target groups could increase some neuronal oscillation during tasks, would that have behavioral consequences? Although we hypothesized that there would be, even if there would not be a behavioral benefit, we would gain important, fundamental insight in different neuronal mechanisms to shape human cognition.

In sum, we conclude that many more studies need to be conducted and reproduced, in both young, healthy and other target groups, to elucidate the role of and effects of manipulation of neuronal oscillations on behavior. Further insight from fundamental research into neuronal mechanisms is required to develop robust products for augmenting cognition.

Chapter 6

Interregional theta and alpha band synchronization reflects fronto-striatal and striato-frontal interactions in humans

This chapter is based on

Horschig, J.M., Smolders, R., Bonnefond, M., Schoffelen, J., van den Munckhof, P., Schuurman, P.R., Cools, R., Denys, D., Jensen, O. *(submitted)*, Directed communication between nucleus accumbens and neocortex in humans is differentially supported by synchronization in the theta and alpha band

Summary

Anatomically, the ventral striatum (VS) is strongly connected with the neocortex (Alexander et al., 1986; Haber, 2003; Haber et al., 1995). However, currently there is little known about the neuronal dynamics supporting the communication between striatum and neocortex. Earlier studies utilizing electrodes implanted in human subcortical regions have reported on theta (4-7 Hz) and alpha (9-14 Hz) band oscillations in the VS (Axmacher et al., 2010; Cohen et al., 2009, 2008a; Lega et al., 2011), as well as coherence between VS and frontal electrodes in the theta band. Here, we report evidence for oscillatory bi-directional interactions between the ventral striatum (VS) and the neocortex in humans. Six patients performed a demanding covert visual attention task while we simultaneously recorded brain activity from electrodes implanted in the bilateral VS and the electroencephalogram (EEG). Both theta and alpha oscillations were strongly coherent with the EEG in frontal and parietal electrodes during the task. Theta-band coherence strongly increased during processing of the visual stimuli. Granger causality analysis revealed that the VS was driving the neocortex in the theta band, while the cortex and the VS were driving each other in the alpha band. Our results are consistent with the notion that the striatum gates behavioral relevant information to cortical areas (Frank et al., 2001; Hazy et al., 2007; O'Reilly and Frank, 2006). We suggest that VS and cortex are mutually suppressing each other prior to stimulus processing as reflected by strong alpha band. Theta oscillations from VS to the cortex then facilitate the active exchange of behaviorally relevant stimulus information.

6.1 Results

Recordings from deep brain electrodes implanted in humans for psychiatric treatment of neurological disorders provide a rare opportunity to investigate subcortico-cortical dynamics. Deep-brain stimulation of the ventral striatum (VS) has been successful in treatment of refractory-resistant obsessive compulsion disorder (Denys et al., 2010; Huff et al., 2010), major depressive disorder (Bewernick et al., 2012; Blomstedt et al., 2011; Giacobbe et al., 2009; Grubert et al., 2011; Nauczyciel et al., 2013; Schlaepfer and Bewernick, 2013) and also drug addiction (Luigjes et al., 2012; Pierce and Vassoler, 2013). We investigated data from six patients (four with OCD, one with major depression disorder and one suffering from drug addiction) with implanted deep brain electrodes in bilateral VS. Prior to stimulation we recorded data simultaneously from the intracranial electrodes and extracranial EEG. All the reported results are from the left VS. Data from the right VS was more noisy and incomplete in some patients. Patients performed a demanding, non-symptomic attention task without any response feedback or reward. Patients had to continuously attend one hemifield and report the color of shortly presented boxes, until a stimulus change at the unattended side occurred. The onset of the stimuli was predictable: after a 1200 ms prestimulus period, two boxes were shortly presented for 33 ms. The patients had to discriminate the color of the box on the attended side, while the unattended square was grey. In some trials, the box at the unattended side was colored as well, and the subjects had to switch attended side and report the color of the box presented on that side. From then on the patients had to attend that side. In this study we specifically investigated how theta-band and alpha-band oscillations supported the functional connectivity between the striatum and the cortex, both in anticipation of and in response to the stimulus.

Spatial topography of coherence

First, we investigated frontostriatal connectivity by computing coherence for the time window from 1000 ms to 500 ms relative to stimulus onset (Rosenberg et al., 1989). Figure 1A shows two clearly distinct peaks, one in the theta-frequency range from 4 to 7 Hz and the other one in the alpha-frequency range from 9 to 14 Hz. Coherence values between 4 Hz and 14 Hz are above 0.1, which we used as an estimate of the noise level to define initial frequencies of interest. To test for significance of these frequencies and to assess spatial specificity we performed a cluster-based permutation test on coherence between VS and EEG channels in the frequency range from 4 to 14 Hz (Maris et al., 2007). We found two highly significant

clusters ($p<0.01$), one over the frontal cortex, and another one over parietal cortex, which we subsequently defined as regions of interest (ROIs). Figure 2B and 2C show topographic plots of coherence in the theta- and the alpha-band. Coherence in the theta-band was in general higher than in the alpha-band, and coherence in the frontal ROI was generally stronger than the parietal ROI.

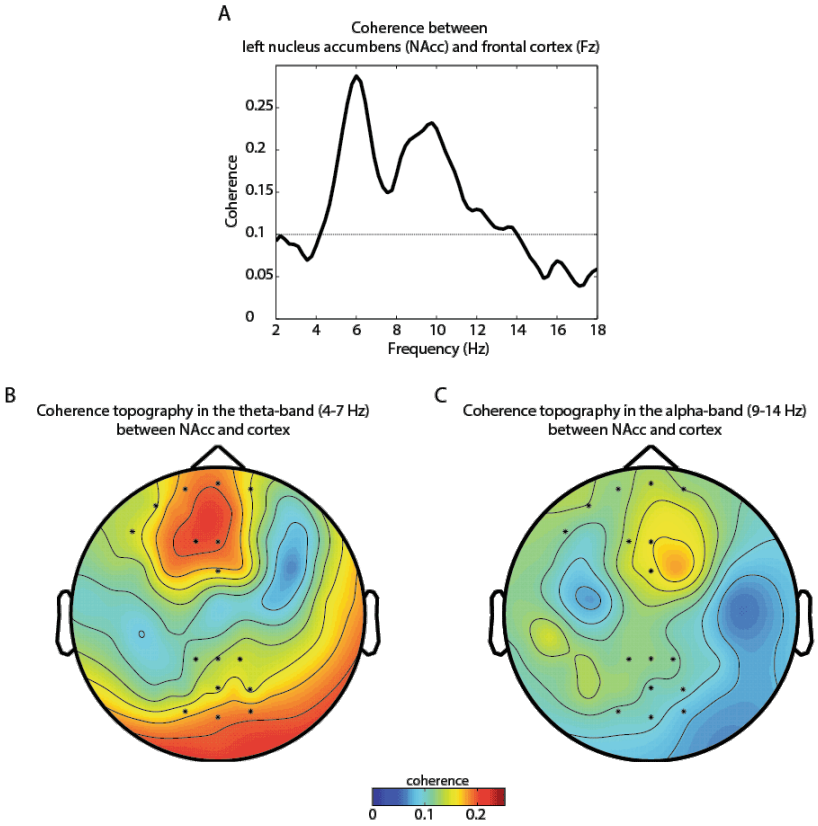


Figure 1 Coherence between the ventral striatum (VS) electrodes and the scalp EEG. **A** Coherence spectrum between VS and a frontal scalp electrode (Fz). There were two clearly visible peaks, one in the theta-band around 6 Hz and the other one in the alpha-band around 10 Hz. The dotted, horizontal line represents a subjective estimate of the coherence floor level. **B** Coherence in the theta-band showed a strong frontal topography and a weaker parieto-occipital topography. **C** Coherence in the alpha-band was strongest around frontal electrodes. The *'s indicate scalp electrodes that were significantly coherent between 4-14 Hz with VS when controlling for multiple comparisons using a cluster randomization approach. A strong frontal and a weaker parietal cluster emerged.

Spectrotemporal dynamics of the oscillatory coupling

Subsequently, we explored the spectrotemporal dynamics of the coherence in response to the stimulus. To this end we conducted a time-resolved coherence analysis from -1000 ms to 500 ms relative to stimulus onset by Hanning-tapered windows 500 ms long. In Figure 2A we show the coherence between sensors in the frontal cluster and the left VS electrodes (marked in Figure 2B and 2C). In the prestimulus interval, we observed strong, sustained coherence in the theta- and alpha-bands. During stimulus processing (~200 ms after stimulus onset), alpha-band coherence decreased whereas coherence in the theta-band increased. This speaks to a functional relevance of cortico-striatal theta- and alpha-band connectivity during stimulus processing.

One might argue that the modulation in coherence is explained by changes in power when comparing the prestimulus (-500 ms to 0 ms relative to stimulus onset) and poststimulus intervals (0 ms to 500 ms relative to stimulus onset). There was no change in power in the theta-band, neither in the VS ($t(5) = -1.12$, p-0.31), nor for the frontal cluster ($t(5)=1.21$, $p=0.28$) nor the parietal cluster ($t(5)=2.27$, $p=0.07$) when comparing these two intervals. In the VS, there was also no change in alpha-power in response to the stimulus ($t(5)=1.00$, $p=0.36$), but a significant alpha-power decrease in the frontal ROI ($t(5)=3.92$, $p=0.01$) and in the parietal ROI $t(5)=3.1$, $p=0.03$).

To further investigate this properties of the functional connectivity, we conducted a time-resolved Granger causality analysis with the same parameters that we used to compute the temporal coherence spectrum (Dhamala et al., 2008a, 2008b; Ding et al., 2006). Figure 2B shows the spectro-temporal dynamics of the Granger causality measured applied to EEG-Fc and VS electrodes. In anticipation of the stimulus, we observed a sustained drive from Fc to VS in the alpha-range. Upon stimulus processing, the alpha-band drive was reduced. In the reverse direction (Fig. 2C), we observed a strong from VS to frontal cortex, sustained drive in the theta-band in both the anticipation and during the processing of the stimulus. During the processing of the stimulus, the theta-band drive further increased.

To access the robustness of the effects we conducted a repeated-measures ANOVA with four factors: *region of interest* (frontal and parietal EEG sensors), *time* (the -500 – 0 ms prestimulus window and the 0 – 500 ms poststimulus window), *frequency* (the 4 – 7 Hz theta band and the 9 – 14 Hz alpha band) and *directionality* (VS to neocortex and neocortex to VS). Granger estimates were log-transformed to approach a normal distribution

(Kolgomorov-Smirnov test; non-log transformed data: $p<0.001$; log-transformed data: $p>0.5$). In the following we report only all significant, or near to significant results from the ANOVA ($p<0.1$). All results are reported in Supplementary Table 1. The ANOVA showed a main effect of frequency ($F(1,5) = 7.68$, $p<0.05$), indicating that Granger causality in the theta-range was generally stronger than in the alpha-range. There was a trend towards a main effect of time ($F(1, 5)=4.78$, $p=0.08$).

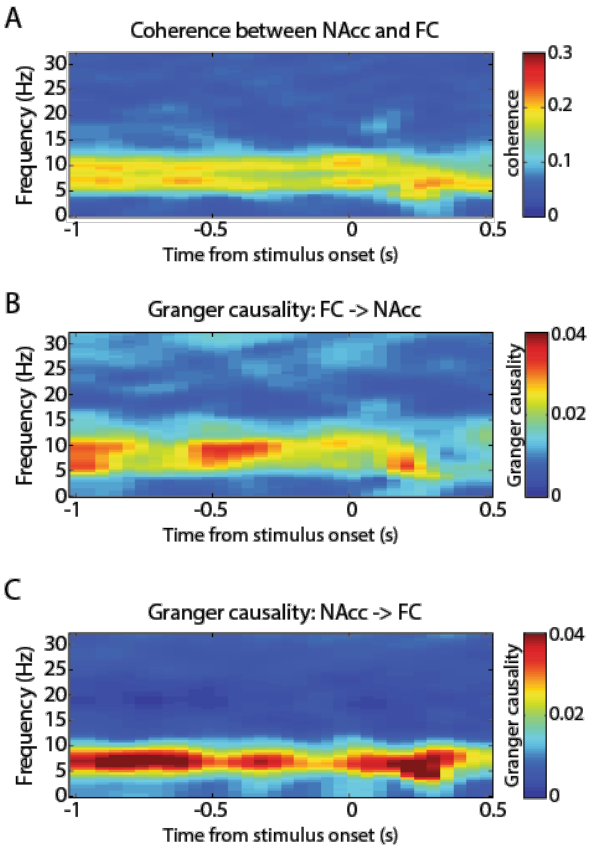


Figure 2 Time frequency dynamics of cortico-striatal interactions between ventral striatum (VS) and frontal cortex (FC). **A** Time-frequency coherence spectrum. In the prestimulus period (-1000 ms to 0 ms), both alpha and theta coherence were strong. After stimulus onset (0 ms), alpha coherence decreased while theta coherence increased. **B** Granger causality from frontal electrodes to VS was highest in the alpha range (9-14 Hz) and diminished upon stimulus processing (after 0 ms). **C** Granger causality from VS to frontal electrodes was strongest in the theta range and increased upon stimulus processing (after 0 ms).

Crucially, we found a significant interaction between *frequency* and *directionality* F(1, 5) = 9.68, p<0.05; see Figure 3A). The significant interaction indicates that the difference in theta-band Granger causality between VS to cortex and cortex to VS was bigger than the same difference in the alpha-range. Post-hoc analysis revealed that Granger causality from VS to cortex was significantly stronger in the theta-band than in the alpha-band (t(5)=4.84, p<0.01). There was no significant difference between theta- and alpha-band causality from cortex to VS (t(5)=1.18, p=0.29). In addition we found that for five of six patients, there was more alpha from cortex to VS than from VS to cortex, which however was not significant (t(5)=1.75, p=0.14).The lack of statistical significant and discrepancy between statistics and visual inspection (Figure 2B and 2C) is most likely caused by the low frequency resolution of the 0.5s time windows, which results in spectral leakage from the theta- into the alpha-band. We conclude that alpha-oscillations facilitate primarily communication from the cortex to the VS, whereas theta-oscillations represent the primary drive from VS to cortex.

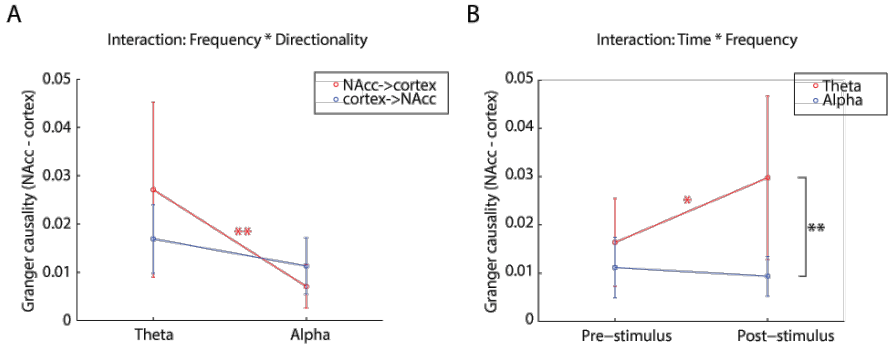


Figure 3 Results of the factorial ANOVA applied to the Granger analysis. **A** The significant *frequency* by *directionality* interaction (F(1, 5) = 9.68, p<0.05) demonstrates that the drive from VS to cortex was stronger in the theta-band than in the alpha-band as confirmed by a posthoc t-test between (t(5)=4.84, p<0.01). **B** The *time* by *frequency* interaction (F(1, 5)=20.92, p<0.01) indicates that the theta increase in the post-stimulus window with respect to the prestimulus window was stronger than the alpha dynamics in time. There was a significant theta increase poststimulus compared to prestimulus (t(5)=3.52, p<0.05). In the poststimulus window, Granger causality in theta was significantly stronger than in alpha (t(5)=4.27, p<0.01). Data are represented as mean ± SEM. * = p<0.05, ** = p<0.01.

In addition we found a significant *time* by *frequency* interaction (F(1, 5) = 20.92, p < 0.01, see Figure 3B). A posthoc analysis revealed that there was a significant theta-band Granger causality increase in the poststimulus interval compared to the prestimulus interval (t(5)=3.52, p<0.05). In contrast, Granger causality in the alpha range showed no significant change in time

(t(5)=-0.08, p>0.9). Furthermore, theta-causality in the post-stimulus interval was stronger than alpha-causality (t(5)=4.27, p<0.01). We suggest that stimulus processing is associated with an increase theta drive from, VS to neocortex.

6.2 Discussion

We investigated how connectivity in corticostriatal networks is implemented by neuronal oscillations in the theta- (4 – 7 Hz) and alpha-band (9 – 14 Hz). Our results show, for the first time, bi-directional temporospectral dynamics between the striatum and the neocortex. We show that the strong coherence in the theta-band observed in our task reflected primarily a drive from VS to the cortex. Furthermore, we show that this connectivity is already present in anticipation of visual stimulation, and increases during stimulus processing. We therefore suggest that theta-band oscillations serve the active exchange of stimulus information. Moreover, corticostriatal connectivity is also implemented by alpha-band oscillations. Alpha-band connectivity reflected connectivity from the neocortex to VS, and was, just like theta activity, present in anticipation of a visual stimulus, but did not increase upon stimulus processing. In fact it rather seemed to decrease. In line with current ideas on the functional role of cortical alpha-oscillations, this might be an inhibitory connection, serving to inhibit ongoing processing in the ventral striatum. We conclude that theta- and alpha-band oscillations serve different functional purposes in cortico-striatal communication.

Cohen and colleagues showed coherence between VS and frontal cortex in the theta-band upon reward processing (Cohen et al., 2009) and during reward anticipation (Cohen et al., 2012). In an earlier study Cohen et al. found preliminary evidence for bidirectional communication between VS and frontal cortex during reward anticipation and reward processing, but did not investigate frequency-specificity (Cohen et al., 2008b). They showed that the directionality of functional connectivity between frontal cortex and VS changed during reward processing: event-related activity in frontal cortex predicted activity in ventral striatum about 100 ms after receiving a reward, and event-related activity in VS predicted activity in frontal cortex around 300 ms after the reward. We extended these findings in showing that theta-band oscillations reflect the active exchange of information between the ventral striatum and the neocortex.

Anatomically, the striatum receives input from different neocortical areas, mainly from temporal and prefrontal areas. Indirectly the striatum projects

back to the prefrontal cortex and parietal cortex via the globus pallidus, subthalamic nucleus and the thalamus (Alexander et al., 1986; Haber, 2003; Middleton and Strick, 2000). Computational models by Frank & O'Reilly (Frank et al., 2001; Hazy et al., 2007; O'Reilly and Frank, 2006) proposed that the dorsal striatum acts as a gatekeeper during working memory tasks. If information should be encoded, the striatum opens the gate and allows stimulus information to enter the prefrontal cortex. During working memory maintenance, the striatum actively shuts down the gate and any intervening information is not passed on to the prefrontal cortex. In contrast to the dorsal striatum, the ventral striatum, or more precisely the ventral striatopallidum, has recently been suggested to be involved in detection of visual information, and an active modulatory role in the amount of neocortical frontoparietal connectivity (van Schouwenburg et al., 2010).

In line with that, we propose a similar mechanism in attention tasks for the ventral striatum. The striatum is under constant bi-directional communication with the neocortex in anticipation of a stimulus. This bi-directional communication is set up by both theta and alpha-oscillations. Upon detection of a behavioral relevant stimulus, the striatum sends information about the stimulus to the cortex, reflected by an increase in corticostriatal theta-band phase synchrony. We hypothesize that this theta-band is associated with behavioral relevant stimuli. Future studies pursuing this issue could test where the degree of behavioral relevance of a given stimulus modulation the theta-band coherence. In our design, behaviorally irrelevant stimuli were simultaneously presented with relevant stimuli, so we were not able to test this hypothesis per se. Presentation of behavioral irrelevant stimuli alone might elicit an increase in alpha-band connectivity between the cortex and the striatum in order to suppress stimulus processing and to prevent information about the stimulus to be exchanged between the cortex and VS. In the past, cortical alpha-band oscillations have been associated with functional, active inhibition of sensory region (Foxe and Snyder, 2011; Jensen et al., 2012; Jensen and Mazaheri, 2010; Klimesch, 2012, 1999; Klimesch et al., 2007). The observed connectivity in the alpha-range might be of inhibitory nature here as well, as there was no modulation upon stimulus processing when an active exchange of information takes place. We propose that inhibitory control might be reflected by an increase in alpha-band corticostriatal connectivity originating in the frontal cortex to actively suppress striatal processing. It has been shown that striatal processing is suppressed upon electrical stimulation of frontal cortex, exerted via hippocampal and thalamic pathways (Calhoon and O'Donnell, 2013). These pathways might be implicated here as well.

The strong influence from the striatum to the neocortex might be surprising, given the polysynaptic connections from the striatum to the neocortex (Alexander et al., 1986; Haber, 2003; Haber et al., 1995). In contrast, the frontal cortex is monosynaptically connected to the ventral striatum, and therefore one might expect a stronger drive from the neocortex to the striatum than the other way around. We, however, found that the control from VS over the cortex was stronger than the control from the cortex over the VS. In rats, McCracken and Grace found that high-frequency stimulation of VS results in stronger low-frequency activity (0.5 – 4 Hz) and beta-activity (13 – 30 Hz) in orbitofrontal cortex (McCracken and Grace, 2009, 2007), which also speaks to a strong, causal influence from VS to neocortex. Likewise in humans, Smolders and colleagues showed that deep brain stimulation in VS results in higher phase stability in the theta range over frontal scalp electrodes in OCD patients compared to when stimulation was turned off (Smolders et al., 2013). Moreover, Antzoulatos and Miller recently showed in monkeys that the striatum (here specifically the caudate nucleus) exerts stronger influence in the beta-band (12 – 30 Hz) on frontal cortex than the frontal cortex does on the striatum (Antzoulatos and Miller, 2014). Our findings match these observations and support the notion that the polysynaptic connections from VS to the neocortex do allow for a strong, causal influence. This influence is most likely exerted via recurrent connections of the thalamus (Haber and Calzavara, 2009)or the hippocampus (Battaglia et al., 2011; Tort et al., 2008).

We investigated a mixed patient population of OCD, depression and drug addiction. This raises the question how our findings translate to the healthy brain, most notably due to patterns of overconnectivity between VS and prefrontal cortex in OCD patients (e.g. Figee et al., 2013). However, the task that the patients performed was kept free from pathological symbols or images to avoid any symptom provoking stimulation. Also behaviorally the patients performed comparable to healthy subjects, which participated in an earlier study with a modified, slightly harder version of the task (see **Chapter 2**).

In conclusion, we presented a study which sheds new light on how functional connectivity in cortico-striatal networks is implemented by neuronal oscillations. Theta- and alpha-band oscillations reflected connectivity in different directions, and served different functional purposes. We proposed that this finding on the ventral striatum is compatible with the ideas from Frank and O'Reilly (Frank et al., 2001; Hazy et al., 2007; O'Reilly and Frank, 2006), who suggested that the (dorsal) striatum acts as a gatekeeper for processing of stimulus information in frontal cortex. This idea is supported by recent investigations of van Schouwenburg et al., who showed

by dynamic causal modeling that the ventral striatopallidum directly influences gating of information by manipulating the degree of frontoparietal connectivity rather than only regional activity (van Schouwenburg et al., 2013, 2010). In future studies, the behavioral relevance of the temporospectral dynamics of corticostriatal connectivity could investigate this further by presenting distracters as well as target stimuli, which allows to study the dynamics of functional gating and the role of the onnectivity between the cortex and VS in the alpha-band.

6.4 Materials and methods

Participants

Seven right-handed patients (one male diagnosed with chronic major depressive disorder, one male cocaine and opiate addict and five female and one male patient with obsessive-compulsion disorder; 22-55 years of age) participated in the experiment after providing written informed consent according to the Declaration of Helsinki and the local Medical Ethical Committee of the Academic Medical Center, University of Amsterdam. All patients underwent surgery for implantation of deep brain electrodes in bilateral ventral striatum (Denys et al., 2010) (VS; illustrated in Figure 4). Data from the male OCD patient was unsuited due to bad data quality.

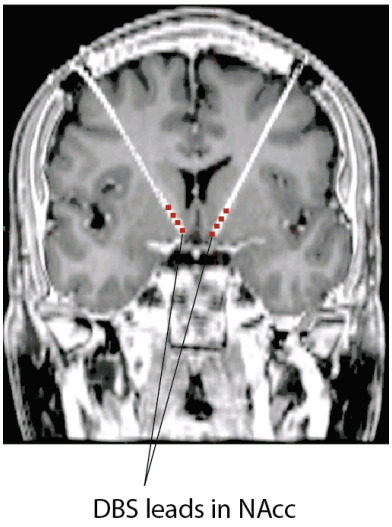


Figure 4 Schematic illustration of deep brain electrodes in bilateral ventral striatum (VS).

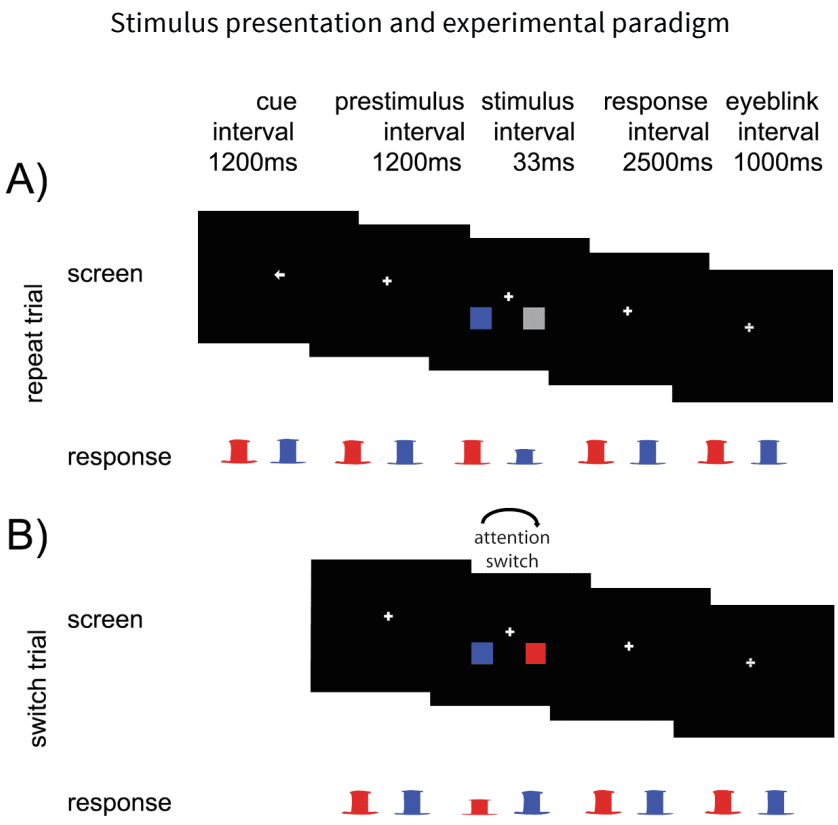


Figure 5 The paradigm. The attended side was initially indicated by a cue. Subjects had to focus at the fixation cross and by button press indicate the color of the attended squares (left button for red and right button for blue). The 1200 ms prestimulus period was followed by the colored stimuli flashed for 33 ms. Subjects had to respond within 2500 ms. If there was a color change in the square of the unattended hemifield, attention had to switch to that direction ('switch-trial). After the response there was a 1000 ms window for eye blinking. A Example of an explicit cue followed by a repeat trial. The subject had to covertly attend to the left and subsequently report the color of the stimuli by pressing the corresponding button (here: blue, right button). B Example of a switch trial. In the previous repeat trials, the subject had to attend to the left, because of the initially shown spatial cue. Upon stimulus presentation, the subject correctly switched attention and indicated so by reporting the color of the stimulus at the formerly unattended side (here: right, red color). If the subject responded according to the formerly attended side (here: left, blue), the switch trial would repeat up to four times. Repetitions of switch trials were removed from the analysis. If the subject did not switch after the fourth consecutive switch trial, another explicit spatial cue pointing to the formerly unattended side was presented (here: a rightward pointing arrow).

EQUIPMENT Stimulus presentation was performed using Presentation (Neurobehavioural Systems, Inc.) and a laptop computer screen (Brand and model, 15 inch display, resolution: 1024 x 768, refresh rate of 60 Hz). The distance to the screen as well as the size of the displayed screen size was kept around 60 cm.

PARADIGM We adapted a covert attention switching paradigm also described in **Chapter 2**, see Figure 5. Squares were flashed on each side and subjects had to report the color of the attended square by a button press. When subjects detected a color change at the unattended side (signaling a *switch trial*), they had to report the color of the unattended square (but not the currently attended square) and switch attention to the unattended side in future trials.

At the beginning of each block, subjects were explicitly cued to which side to attend. From then on, the attended side was determined by stimuli properties alone. A central fixation point was presented during the entire experiment. Colored squares were flashed 1200ms after the beginning of each trial for about 33 ms (two frames=2/60Hz). These stimuli were presented with six degrees eccentricity and two degrees lower than the fixation cross (measured from the fixation cross to the center of the stimuli). The squares were two degrees wide.

Subjects had to report the color of the square on the attended side by pressing a button with their left (for red) or right hand (for blue). On the unattended side, the square was either grey (*repeat trials*) or colored in blue or red (*switch trials*). Subjects had to respond within 2500 ms. After responding, the fixation cross turned grey, indicating that the subject could blink or move the eyes in a 1000 ms period. Then the fixation cross turned white again indicating the start of the next trial. Subjects had to keep attention to one hemifield (*repeat trial*) and report the color of the square on that side until they detected a colored stimulus in the unattended hemifield (switch stimulus). A trial which includes a switch stimulus is called a *switch trial*. The switch stimulus was detected if the color of the unattended target was correctly reported (*detected switch trial*). Subjects then had to keep attending the formerly unattended hemifield until a next switch trial was detected. If a subject failed to detect the switch stimulus (*undetected switch trial*), it was repeated with a random color (blue or red) up to four times. The probability of a switch trial was increasing with the number of trials since the last switch trial, but is not of further importance for this study (see **Chapter 2** for more information).

STIMULUS INTENSITY In order to make the task sufficiently difficult, the intensity of the stimuli was varied across subjects and early trials in an adaptive staircase-like procedure on a 20-step scale (1:darkest; 20:brightest), starting at 10 for both the neutral and the colored stimuli. This was done in the first block (i.e. until the 15th *detected* switch trial). Trials from this block were not included in the later analyses. The intensities of the neutral and colored stimuli were modulated according to different criteria. Repeat trials should be sufficiently demanding while keeping response errors as low as possible. Therefore we kept reducing the brightness of the colored stimuli to a level in which the subject could perform the discrimination with no errors. The color intensity was reduced by one step after each *detected switch trial* and error-free performance. After a response error to repeat trials, the intensity was increased by one step again. The intensity of the neutral stimulus was adapted to manipulate the difficulty of switch trials. A large intensity difference between colored and neutral stimuli makes detection of switch trials easier (pop-out effect), whereas a similar intensity results in a harder task and less detected switch trials. We aimed at a correct response rate to switch trials between 25% and 75%. After a detected switch trial, the neutral stimulus was increased in intensity by one when less than 25% of all switch trials were detected. The intensity was decreased by one step when more than 75% of all switch trials were detected. The twenty levels of stimulus luminance were visually and mathematically matched according to the CIELAB specifications (Rubner et al., 1998; Ruzon and Tomasi, 1999). Note that the adaptation procedure was only applied in the first block until the 15th detected switch trial.

INSTRUCTIONS Prior to the experiment, participants received written and verbal task instructions. Subjects were instructed to prioritize accuracy rather than speed, but were informed that they should respond within 2500 ms. They were instructed to detect the color at the cued side, but switch attention to the uncued side if the color at that side turned from grey to either blue or red. Subjects were informed that they would receive no response feedback. The instructions did not inform about other task properties. After the instructions, subjects had to complete a short tutorial on the computer, which explained the paradigm and introduced the stimuli. Afterwards the experimental task started. In our analysis, as already reported above, we discarded all trials up to the first experimental break.

Data acquisition

The ongoing brain activity was recorded using a 64-EEG-channel recording system (Advanced Neuro Technology B.V.) at a sampling rate of 512Hz following the international 10-10 system. Eight channels were used to rec-

ord the deep brain electrodes near the VS (four electrodes per lead), four to derive horizontal and vertical eye-movement, leaving 52 Ag/AgCl channels distributed evenly on the scalp while leaving out areas covered by post-surgery bandages. Only channels that were common for all patients were included in the final analysis. These were the following 42 channels: AF7, AF8, C1, C2, C3, C4, C5, C6, CP1, CP2, CP3, CP4, CP5, CP6, CPz, Cz, F1, F7, F8, FC5, FC6, FCz, FT7, FT8, Fp1, Fp2, Fpz, Fz, O1, O2, Oz, P1, P2, P3, P4, P5, P6, PO3, PO4, PO7, POz and Pz. Purely for visualization purposes, missing channels were interpolated using a spherical spline interpolation (Perrin et al., 1989).

Data preprocessing and analysis

PREPROCESSING The EEG data were analyzed using the Matlab-based FieldTrip toolbox, developed at the Donders Institute for Brain, Cognition and Behaviour (Oostenveld et al., 2011). Muscle and ocular artifacts were detected in a semi-automatic fashion, which included visual inspection and trial rejection based on variance and other measures as implemented in FieldTrip. We rejected all trials with an artifact in the window from -1000 ms to 500 ms relative to stimulus onset.

To estimate activity of the left and right VS, we computed the bipolar derivative of the deepest and the second deepest deep brain electrode for the left and right lead, respectively. We will refer to these as left and right VS. For the main manuscript, only data from the left VS were used. Thus "VS" refers to the bipolar derivative of left VS. Data from the right VS showed more noise, therefore less reliable results. In addition, no data for the right VS was recorded in one patient. We therefore decided to conduct no further analysis on the data from the right VS.

SPECTRAL ANALYSIS We computed Fourier coefficients from 0 Hz to 256 Hz for three time windows: the whole trial window from -1000 ms to 500 ms relative to stimulus onset, the prestimulus window from -500 ms to 0 ms, and the poststimulus window from 0 ms to 500ms. All data windows were zero-padded by 4500 ms to smooth the Fourier estimates and avoid sudden transitions, especially around the 50 Hz noise-band. This resulted in a frequency resolution of 0.16 Hz for the whole trial window and 0.2 Hz for the pre- and poststimulus windows. For visualization, we show only the content from 2 to 18 Hz.

We computed the time-frequency representations (TFRs) of power from 0 to 256 Hz (0.5 Hz increments) for each trial from a -1000 ms to 500 ms interval around the stimulus onset. Spectral content was estimated using a

500 ms time window, which was multiplied with a Hanning window prior to applying a fast Fourier transform. For visualization, we only show the low frequencies up to 30Hz.

COHERENCE ANALYSIS We computed the squared coherence for each combination of the VS and extracranial EEG channels. Coherence $C_{xy}(f)$ between two signals x and y is computed the using the power spectra of both channels $S_{xx}(f)$ and $S_{yy}(f)$ and their cross-spectrum $S_{xy}(f)$ by the following equation (Rosenberg et al., 1989):

$$C_{xy}(f) = \frac{|S_{xy}(f)|^2}{\left(S_{xx}(f)S_{yy}(f)\right)} \quad (1)$$

A coherence $C_{xy}(f)$ of *0* indicates that the signals x and y have no phase relationship, whereas a value of *1* indicate that the two signals are fully phase-coherent.

NON-PARAMETRIC GRANGER CAUSALITY Granger causality in the time-domain is well defined and has been well-established throughout the last century (Granger, 1969; Wiener, 1956). From the time-domain formulation of Granger causality, one can directly infer a formulation for non-parametric Granger causality in the frequency domain (Dhamala et al., 2008a, 2008b; Ding et al., 2006; Geweke, 1984). We summarize the most important aspects of this derivation here and outline its relation to coherence as explained above.

A signal x is said to Granger cause signal y if the future of signal y can be better explained by incorporating knowledge about the past of signal x.

Total interdependence $f_{x,y}(f)$ between of two signals x and y is computed by their power spectra $S_{xx}(f)$ and $S_{yy}(f)$ and their cross spectra $S_{xy}(f)$ as

$$f_{x,y}(f) = \ln\left(\frac{S_{xx}(f)S_{yy}(f)}{|S(f)|}\right) \quad (2)$$

where *ln* denotes the natural logarithm, and $S(f) = S_{xx}(f)S_{yy}(f) - S_{xy}(f)S_{yx}(f)$. From equation (1) and (2), one can infer that

$$f_{x,y}(f) = -\ln\left(1 - C_{xy}(f)\right) \quad (3)$$

Furthermore, total interdependence can be decomposed into three different causality terms:

$$f_{x,y}(f) = \mathrm{f}_{\mathrm{x}\to\mathrm{y}} + \mathrm{f}_{\mathrm{y}\to\mathrm{x}} + \mathrm{f}_{\mathrm{x}\cdot\mathrm{y}} \quad (4)$$

Where $f_{x\to y}$ denotes the causal influence from signal x to signal y, $f_{y\to x}$ denotes the causal influence from signal y to causal x and $f_{x\cdot y}$ denotes the *instantaneous causality*, i.e. by non-linear interaction between x and y or by any contributions exogenous to signal x and y, for example common input from a third signal.

From the derivations of Geweke (1984) and Ding et al. (2006) follows that

$$f_{x\to y}(f) = -\ln\left(\frac{S_{xx}(f)}{\tilde{H}_{xx}\Sigma_2\tilde{H}_{xx}^{*}}\right) \tag{5}$$

$$f_{y\to x}(f) = -\ln\left(\frac{S_{yy}(f)}{\tilde{H}_{yy}\Gamma_2\tilde{H}_{yy}^{*}}\right) \tag{6}$$

where $\boldsymbol{\Sigma}_2$ and $\boldsymbol{\Gamma}_2$ denote the variance of the noise-term in the bivariate model of signal x and y, respectively (i.e. can be obtained from their noise covariance matrix $\boldsymbol{\Sigma}$), $\tilde{H}_{xx}$denotes the spectral transfer function of signal x after normalization, and * the complex conjugate. The instantaneous causality can be thus considered as the difference between squared coherence and the sum of the two causality terms $f_{x\to y}$ and $f_{y\to x}$. For a more thorough derivation see Geweke (1984) or Ding et al. (2006).

The normalized spectral transfer function $\tilde{H}_{xx}$ of signal x can be derived using a matrix factorization method from the spectral representation of signal x and y(Wilson, 1972). Note that the spectral representations S_{xx} and S_{yy} can also be fully estimated by the normalized spectral transfer function $\tilde{H}_{xx\,xx}$ and $\tilde{H}_{yy\,yy}$ and the noise-covariance matrix $\boldsymbol{\Sigma}$. It should be noted that the instantaneous causality term can become negative for “certain situations” and that it thus might not have a “readily interpretable physical meaning” (Ding et al., 2006, p. 10).

STATISTICAL ANALYSIS Statistical significance of the coherence of the neural data was assessed using a non-parametric cluster-based permutation test (Maris et al., 2007; Maris and Oostenveld, 2007). In the cluster-based permutation test, notational significant clusters in channel/grid space are detected using a parametric test-statistic, here the t-statistic thresholded by an uncorrected threshold. In accordance to (Maris et al., 2007), if there are more than 20 degrees of freedom and if the squared population coherence is between 0.4 and 0.95, then $\tanh^{-1}\left(C_{xy}(f)\right)$ is approximately normal distributed with mean $\tanh^{-1}\left(C_{xy}(f)\right) - {}^{1}/_{(df-2)}$ and variance ${}^{1}/_{(df-2)}$. Thus, a standard z-transformation can therefore be performed to obtain z-transformed coherence Z_{xy} as follows:

$$Z_{xy} = \frac{\tanh^{-1}\left(C_{xy}(f)\right) - {}^{1}/_{(df-2)}}{\sqrt{{}^{1}/_{(df-2)}}} \quad (7)$$

Note that although above mentioned requirements are not met in our data, this is no reason for concern as we applied the here described nonparametric test. This transformation was, however, done to account for the different amount of degrees of freedom (#trials) across subjects.

As we did not analyze any condition contrast, we compared the observed z-transformed coherence Z_{xy} with a surrogate distribution of maximal z-transformed coherence cluster sizes. One instance of the surrogate distribution was computed as follows: For each patient, we randomly shuffled trials from the intracranial data, while remaining the order of trials of the EEG data. Then, we computed the z-transformed coherence Z_{xy} for each patient of this shuffled order, and computed grand-average z-transformed coherence across patients. This was conducted 500 times to obtain a surrogate distribution. A cluster-based permutation test therefore controls for multiple comparisons. To determine the regions of interest, we averaged over time and frequency of interest (here -1s to 0.5s, and 4 Hz to 14 Hz) to yield clusters only in channel space. We considered a cluster to be significant when the absolute difference in summed cluster size exceeded 3.92, which is twice the threshold at alpha = 2.5%.

Chapter 7

General Discussion

Throughout the last decades, a strong functional role of alpha oscillations has been identified - functional inhibition of neuronal ensembles (see **Chapter 1** for more details). In this thesis, I make use of this property of posterior alpha oscillations by using covert visual spatial attention tasks (in short covert attention) Attending to one visual field while ignoring the other results in a posterior, hemispheric alpha lateralization that serves to inhibit information coming from the unattended hemifield and allows for processing of the attended information. Thereby, this alpha lateralization reflects the degree of visuospatial attention (Kelly et al., 2009; Thut et al., 2006; Worden et al., 2000). In the past it has been shown that the strength of the alpha lateralization differs among individuals, which in turn reflects the individual ability to ignore the unattended visual field (Händel et al., 2011). Individuals that showed a strong alpha lateralization only saw salient visual stimuli in the unattended visual field, whereas participants with a weak alpha lateralization also saw less salient stimuli. This suggests that the degree of alpha lateralization and the ability to ignore visuo-spatially presented information reflects an individual trait.

These individual differences also become apparent in daily life, where we have to adapt to the environment in a flexible manner. At some points in time, being attentive is more important than at others, and crucially, some people are better in adapting their attentional state to the environment than others. In **Chapter 2** I investigated whether the degree of visual attention changes with the likelihood of an upcoming stimulus at an unattended location. I measured both behavioral performance as well as the degree of alpha lateralization during the task. Participants had to covertly attend to one hemifield until a stimulus change at the unattended hemifield occurred (*switch trial*). If a switch trial was detected, they had to covertly switch attention. Crucially, the likelihood of a switch trial was underlying a linear likelihood model (*switch trial likelihood*). Participants were not explicitly informed about the switch trial likelihood. Yet, I showed that participants were able to infer the switch trial likelihood while performing the task. This ability differed among individuals. Most importantly, if a participant modulated his posterior alpha rhythm according to the switch trial likelihood, he was better able to detect a switch stimulus the higher the switch trial likelihood was. This finding emphasizes the importance of adjusting posterior alpha-band oscillations to environmental statistics for optimal task performance. Recently, Gould et al. (2011) showed that the degree of posterior alpha lateralization is modulated according to explicit environmental task properties. I extend that finding by showing that individuals are also able to do so for properties they have to infer from the en-

vironment. However, this study also shows that optimal adjustment to the environment is not achieved by all individuals.

Following, I asked if the individual ability to modulate the posterior alpha-rhythm can be trained. I developed an MEG brain-computer interface using the posterior alpha rhythm in a covert attention task, and trained participants in four sessions to modulate their alpha rhythm, while laterally presenting feedback on their current level of alpha lateralization. In **Chapter 3** I showed that participants could learn to voluntarily modulate their posterior alpha lateralization within a single session of less than ten minutes. Further, participants significantly improved in controlling their alpha lateralization after the first session. These findings show that conscious modulation of posterior alpha lateralization is possible and that this ability can be trained. This study also indicates the suitability of using alpha-oscillations for brain-computer interfacing, as it is a reliable control signal that is easy and fast to learn. As such it might be a promising paradigm in paralyzed patients. In contrast to the widely used imagined movement (Wolpaw et al., 1991) or visual P300-paradigms (Farwell and Donchin, 1988), covert attention does not require eye movements or vivid imagery of muscle movement, which fully locked-in patients are not capable of (Birbaumer and Cohen, 2007). Therefore, the paradigm used in **Chapter 3** might be a suitable alternative where other BCI paradigms fail.

The study presented in **Chapter 3** also demonstrates that investigations from the field of cognitive neuroscience can help to identify reliable control signals for the field of brain-computer interfacing. These insights can help to embed the BCI training in a natural environment to modulate the control signal as for example done here. Covert attention modulates the posterior alpha rhythm, thus it is most natural that participants should learn to control their posterior alpha rhythm in a covert attention paradigm. Furthermore, given the strong correlation in covert attention tasks between behavioral performance and the degree of alpha lateralization (see e.g. Kelly et al., 2009; Thut et al., 2006), next I asked whether training to control the posterior alpha lateralization has consequences for behavioral performance. This would speak to a causal relationship between the degree of posterior alpha lateralization and cognitive performance during covert attention tasks.

In **Chapter 4** I built a hypothesis-driven brain computer interface with the goal to investigate the effects of BCI training based on alpha lateralization on behavioral performance. Forty participants received either feedback on their posterior alpha rhythm or received sham feedback. Crucially, participants were only trained on attention to the left or attention to the right

hemifield. The key finding was that those subjects who received neurofeedback training became worse in attending to the untrained hemifield. In other words, I trained participants to actively ignore the untrained hemifield. This was again achieved by about 10 minutes of neurofeedback training. The group of participants who received sham feedback did not show any behavioral modulation by the unilateral training. This study adds to the evidence suggesting a causal relationship between alpha oscillations and cognitive performance in covert attention tasks.

In future, these insights can lead to interesting training paradigms serving to reduce attention deficits: we can train participants to ignore a particular part of visual input. For example, ADHD patients show a lack of sustaining a high degree of alpha lateralization when attending to the left visual field (ter Huurne et al., 2013). In **Chapter 3** I presented evidence that the degree to which individuals can control their alpha lateralization can be trained. Thus, ADHD patients might be able to learn to maintain a high degree of alpha lateralization by this paradigm. In combination with the findings of **Chapter 4**, one might also expect an increased ability to ignore distracting information. In **Chapter 5** this and related suggestions for future research were presented. There I summarized recent evidence in favor of these suggestions, and discussed related techniques such as transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS). Furthermore, I discussed applications for different target groups, and critically assessed practical considerations of these approaches.

Finally, in **Chapter 6** I investigated how corticostriatal networks interact with cortical oscillations. Recently, it was found that the striatum directly modulates the degree of frontoparietal connectivity during visual detection tasks (van Schouwenburg et al., 2013, 2010). The findings in **Chapter 2**, **Chapter 3** and **Chapter 4** showed that posterior alpha-oscillations are under strong top-down control, i.e. modulated by other brain regions involved in expectation and intention. Frontal regions around FEF and parietal regions around the intraparietal sulcus (IPS) have been identified as top-down control regions of posterior alpha oscillations by interventional studies using TMS (Capotosto et al., 2012a, 2009; Sauseng et al., 2011). As such, there is evidence that the degree of frontoparietal connectivity influences the allocation of posterior alpha oscillations, which in turn is modulated by the striatum. Therefore, I investigated the involvement of theta- and alpha-band oscillations in striato-cortical and cortico-striatal interactions during a covert attention task in **Chapter 6**. In cooperation with the academic medical centre in Amsterdam (*Academisch Medisch Centrum Amsterdam*), I conducted an experiment in patients with implanted deep-brain electrodes in the ventral striatum (VS). Simultaneously to the intra-

cranial electrodes, we recorded from scalp electrodes and investigated how the VS and the neocortex interact with each other. I found that the VS interacts with the frontal and parietal cortex in two frequency-bands: the theta-band and the alpha-band. In this study, I showed for the first time that human corticostriatal networks employ different frequency bands for bi-directional communication. Further, I proposed that the ventral striatum acts as a gatekeeper during attention task in a similar manner as the dorsal striatum does during working memory. According to this proposal, information is passed on from the ventral striatum to the frontal (see e.g. Alexander et al., 1986) and parietal cortex (Saint-Cyr et al., 1990) in the theta-band, while alpha-band oscillations help to suppress processing in anticipation of visual information.

7.1 Broader implications and outlook

In this thesis, I provided evidence that alpha oscillations are not just a by-product of cognition, but that they are causally involved in cognition (**Chapter 4**). While conventional neuroimaging studies cannot disentangle correlational from causal relations, interventional techniques allow for more powerful hypotheses. Transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS) are such interventional techniques (introduced and reviewed **Chapter 5.3**). Several TMS studies have provided evidence for a causal role of alpha oscillations in working memory (Klimesch et al., 2003b) and covert visual attention (Romei et al., 2010; Sauseng et al., 2011). In light of these findings, Hanslmayr et al. (2005b) successfully mimicked the effects found by Klimesch et al. (2003b) using BCI. In a similar vein, in **Chapter 4** I showed that BCI also allows attributing a causal role to alpha lateralization during covert visual attention, thereby corroborating the recent claims. In **Chapter 5.3**, I refer to this idea behind brain-computer interfacing as hypothesis-driven brain-computer interfacing (hdBCI).

The goal of hdBCI is comparable to interventional approaches like TMS or tCS. By directly manipulating ongoing neural oscillations, stronger conclusions about the involvement of the manipulated neuronal oscillations in cognition can be made. The goal of hdBCI is twofold. First, we can regard BCI as a technique to make stronger hypotheses about cognition. We can test whether the control signal, e.g. alpha oscillations, is causally involved in cognition. Note that such a hypothesis can only be made if there is already strong correlational evidence. Second, if there is evidence for such a strong, causal relationship between the control signal and an aspect of cognition, then hdBCI can be used to specifically augment that aspect of

cognition. In **Chapter 5**, I identified areas of cognition that could be augmented and discussed applicability in several target groups.

Establishing causal links between neuronal oscillations and cognition is not only a prerequisite for augmentation, but also to pave the way for treatment of neurophysiological disorders. Thereby, such empirical investigations might also help to inform conventional neurofeedback approaches, which are nowadays already used to e.g. reduce symptoms of ADHD patients (Arns et al., 2009; Lubar et al., 1995), but with arguable success (Vollebregt et al., 2013). In **Chapter 4** and **Chapter 5.4**, I explicitly proposed that hdBCI training on alpha lateralization might be beneficial for patients suffering from ADHD. The behavioral training effects found in **Chapter 4** suggest that I trained participants to inhibit information presented at the unattended hemifield. As such, this training effect is desirable for treating inattentiveness in ADHD patients as well as in the elderly, who also have problems with excessive distraction (as also reviewed in **Chapter 5**).

However, there are a number of unknowns at this moment that need to be investigated first before trying to treat such disorders. First of all, long-term effects of the hdBCI training need to be assessed. In **Chapter 3**, I showed that participants were able to maintain the trained ability to control their alpha lateralization for several days, but I did not investigate whether this ability can be unlearned, or whether it can be further increased by more intensive training. Furthermore, I did not investigate how long the behavioral effects last that I reported in **Chapter 4**. For successful treatment of attention deficits, a sustained, long-term effect is required (Arns et al., 2009). Additionally, it is unknown whether the training results in terms of alpha lateralization neurofeedback and behavior will be comparable to healthy individuals in other target groups. In **Chapter 5.3**, I proposed that the functional role of neuronal oscillations might be different and partly substituted by other neuronal mechanisms in ADHD patients and in the elderly. This hypothesis arose from the observation that correlations between behavioral variables and neuronal oscillations were absent in ADHD patients and the elderly, while being strongly present in young, healthy individuals. Still, ADHD patients and the elderly are able to successfully conduct attention tasks, and also show attentional effects of cues (see **Chapter 5.3**). Thus, it remains a long path until we can conclude that neurofeedback training on neuronal oscillations can be used as a successful treatment for these patient groups. However, a first step has been taken here in showing that the hypothesized functional role of neuronal oscillations is indeed coupled to behavioral performance in young, healthy adults. As a next step I propose to study long-term effects in young, healthy individuals before studying whether our knowledge on neuronal oscilla-

tions and human cognition can be applied to other target groups, such as ADHD patients and the elderly.

Apart from long-term effects on alpha lateralization and related visual attention performance, also plastic changes in the brain might occur by longer training. By modulating the degree of posterior alpha lateralization in BCI settings as in **Chapter 3** and **Chapter 4**, also top-down interactions are inevitable modulated. Therefore, long-term BCI training could have a sustained influence on patterns of functional connectivity as well. The influence of BCI training on whole brain networks has only recently attracted attention. Preliminary evidence suggests that BCI training on neuronal oscillations indeed alters functional connectivity in the brain (Ros et al., 2013). As discussed above, candidate regions modulating the posterior alpha rhythm are the frontal eye fields (FEF) and the intraparietal sulcus (IPS). It would be interesting to investigate whether the BCI paradigms used in **Chapter 3** and **Chapter 4** also modulate the degree of frontoparietal connectivity. Similar to the approach by Ros et al. (2013), patterns of functional connectivity could be assessed by functional magnetic resonance imaging (fMRI), and then correlated with the training effect. Here, modulated functional connectivity in the dorsal attention network including FEF and IPS can be expected. Additionally, in light with the findings of **Chapter 6** and with the studies by van Schouwenburg et al. (2013, 2010), it might be interesting to investigate whether the effect of the striatum on the strength of frontoparietal connectivity is influenced as well.

In addition not only patterns of functional connectivity might have been influenced by the BCI training, but also the anatomical changes might occur after several sessions. There is strong evidence that properties of neuronal oscillations are related to anatomical factors. Biophysical considerations suggest that the strength and length of white fiber tracts do affect conduction speed, and might thereby influence oscillatory peak frequencies (Hursh, 1939; Nakagawa et al., 2014). Valdes-Hernandez et al. (2010) showed that alpha peak frequency indeed correlates positively with white matter density along ipsilateral longitudinal tracts and negatively along contralateral longitudinal tracts. In addition, recently Marshall et al. (personal communication) found that the degree of alpha lateralization correlates with the thickness of superior longitudinal tracks. Yet, these findings do not answer whether the thickness of these fiber tracts are a cause or a consequence of oscillatory power. In future, a direct investigation of this relationship might be possible using the here presented BCI paradigms in combination with diffusion tensor imaging (DTI) to measure the thickness of fiber tracts. There is preliminary evidence that BCI training on the beta rhythm (15-18 Hz) over several weeks indeed has an effect

on white matter density (Ghaziri et al., 2013). Future investigations could investigate whether a similar effect also occurs in response alpha lateralization BCI training.

In the early days of electrophysiological brain recordings, alpha-band oscillations were hypothesized to present an idling rhythm of the brain (Adrian and Matthews, 1934; Berger, 1929), i.e. if the brain has nothing to do, there is high alpha activity. In the last years, a number of investigations have led to a different hypothesis of alpha oscillations in which they are taking an active, functional role. The contemporary hypothesis states that alpha-band oscillations represent the active inhibition of brain regions (Foxe and Snyder, 2011; Jensen and Mazaheri, 2010; Klimesch, 1999; Klimesch et al., 2007). Thereby, alpha oscillations are said to gate the flow of information in the brain: regions that are showing low alpha power may process and transmit information, and streams to regions which expose high alpha power become inefficient. Thus, the flow of information in our brain is determined by the amount of top-down controlled inhibition, partly reflected by the distribution of cortical alpha oscillations.

While alpha oscillations are strongly involved in gating the flow of information, they are not the only gatekeeper in the human brain. Classically it has been proposed that the striatum is involved in working memory processes and forms a functional network with the prefrontal cortex. In this network the prefrontal cortex maintains information in working memory and the striatum is responsible for selection and gating of information (Frank et al., 2001; Hazy et al., 2007; O'Reilly and Frank, 2006). These roles are directly supported by lesion studies, which also show hemispheric specificity. A lesion in the right frontal cortex result in a general loss in working memory capacity, whereas a lesion in the left putamen (i.e. left striatum) impairs working memory performance specifically when a target is presented simultaneously with distracters (Baier et al., 2010). This left hemispheric specialization of the basal ganglia for filtering of information was also observed by McNab and Klingberg in an fMRI study in healthy individuals (2008). While these observations and theories are explicit to only the dorsal striatum, it has also been argued that a similar interaction might occur for the ventral striatum when it comes to motivational responses and long-term reward values (Frank et al., 2007; Frank and Claus, 2006). In fact, recently Fallon and Cools (2014) found that during positive rewards, an increased BOLD signal in the ventral striatum and PFC represents a "closed gate" process: while distractors had less influence during WM encoding, also updating of working memory was impaired, or in other words, the striatum did not allow for updating of information in working memory. The ventral striatum might thus also take such a gatekeeper

role in attention processes, which is in line with van Schouwenburg et al. (2013, 2010).

In **Chapter 6**, I showed that alpha-oscillations are directly involved in striatocortical interactions. This suggests that the gatekeeping role of alpha-band oscillations and of the striatum might complement each other. However, the precise role of these different gatekeepers remains uninvestigated so far. To investigate this further, a combined EEG and fMRI study could help to identify whether the inhibitory role of alpha oscillation and the gatekeeping mechanism of the striatum are mutually interacting or complementary to each other. Van Schouwenburg et al. (2013, 2010) proposed that the striatum directly manipulates frontoparietal interactions. Therefore one might expect that the gating mechanism in the striatum and neocortical alpha oscillations are in versatile interaction with one another, possibly mediated by frontoparietal top-down control networks of posterior alpha oscillations.

7.2 Conclusion

In this thesis, I explored individual abilities to flexibly modulate and learn to control cortical alpha-band oscillations, and investigated whether they are involved in corticostriatal communication. I identified that modulating the degree of posterior alpha lateralization strongly differs among individuals, but that this ability can be trained by brain-computer interface training. Furthermore I showed that successful BCI training on modulating the degree of alpha lateralization results in a subsequent change in behavioral performance. Thereby I corroborated current evidence speaking to a causal role of alpha oscillations in cognition. Furthermore, I discussed this BCI approach, which I coined hypothesis-driven BCI (hdBCI), and other interventional approaches in an extensive manner. Finally, I also shed light on how corticostriatal networks are interacting in the theta- and alpha-band. By this series of studies I have paved the way for further investigations in the field of hypothesis-driven brain-computer interfacing and related interventional approaches. In future such approaches allow stronger, functional hypotheses in empirical studies, and could lead to promising treatment options for a variety of disorders such as ADHD

Appendix

References

Adams, R., Finn, P., Moes, E., Flannery, K., Rizzo, A.S., 2009. Distractibility in Attention/Deficit/ Hyperactivity Disorder (ADHD): the virtual reality classroom. Child Neuropsychol. J. Norm. Abnorm. Dev. Child. Adolesc. 15, 120–135. doi:10.1080/09297040802169077

Adams, Z.W., Derefinko, K.J., Milich, R., Fillmore, M.T., 2008. Inhibitory functioning across ADHD subtypes: recent findings, clinical implications, and future directions. Dev. Disabil. Res. Rev. 14, 268–275. doi:10.1002/ddrr.37

Addante, R.J., Watrous, A.J., Yonelinas, A.P., Ekstrom, A.D., Ranganath, C., 2011. Prestimulus theta activity predicts correct source memory retrieval. Proc. Natl. Acad. Sci. U. S. A. 108, 10702–10707. doi:10.1073/pnas.1014528108

Adrian, E.D., Matthews, B.H.C., 1934. The Berger Rhythm: Potential Changes from the Occipital Lobes in Man. Brain 57, 355–385. doi:10.1093/brain/57.4.355

Alain, C., Woods, D.L., 1999. Age-related changes in processing auditory stimuli during visual attention: evidence for deficits in inhibitory control and sensory memory. Psychol. Aging 14, 507–519.

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel Organization of Functionally Segregated Circuits Linking Basal Ganglia and Cortex. Annu. Rev. Neurosci. 9, 357–381. doi:10.1146/annurev.ne.09.030186.002041

Allendorfer, J.B., Storrs, J.M., Szaflarski, J.P., 2012. Changes in white matter integrity follow excitatory rTMS treatment of post-stroke aphasia. Restor. Neurol. Neurosci. 30, 103–113. doi:10.3233/RNN-2011-0627

Andrés, P., Parmentier, F.B.R., Escera, C., 2006. The effect of age on involuntary capture of attention by irrelevant sounds: a test of the frontal hypothesis of aging. Neuropsychologia 44, 2564–2568. doi:10.1016/j.neuropsychologia.2006.05.005

Antal, A., Paulus, W., 2013. Transcranial alternating current stimulation (tACS). Front. Hum. Neurosci. 7. doi:10.3389/fnhum.2013.00317

Antzoulatos, E.G., Miller, E.K., 2014. Increases in Functional Connectivity between Prefrontal Cortex and Striatum during Category Learning. Neuron 83, 216–225. doi:10.1016/j.neuron.2014.05.005

Arns, M., Heinrich, H., Strehl, U., 2014. Evaluation of neurofeedback in ADHD: the long and winding road. Biol. Psychol. 95, 108–115. doi:10.1016/j.biopsycho.2013.11.013

Arns, M., Ridder, S. de, Strehl, U., Breteler, M., Coenen, A., 2009. Efficacy of Neurofeedback Treatment in ADHD: The Effects on Inattention, Impulsivity and Hyperactivity: A Meta-Analysis. Clin. EEG Neurosci. 40, 180–189. doi:10.1177/155005940904000311

Axmacher, N., Cohen, M.X., Fell, J., Haupt, S., Dümpelmann, M., Elger, C.E., Schlaepfer, T.E., Lenartz, D., Sturm, V., Ranganath, C., 2010. Intracranial EEG correlates of expectancy and memory formation in the human hippocampus and nucleus accumbens. Neuron 65, 541–549. doi:10.1016/j.neuron.2010.02.006

Bahramisharif, A., van Gerven, M., Heskes, T., Jensen, O., 2010. Covert attention allows for continuous control of brain-computer interfaces. Eur. J. Neurosci. 31, 1501–1508. doi:10.1111/j.1460-9568.2010.07174.x

Baier, B., Karnath, H.-O., Dieterich, M., Birklein, F., Heinze, C., Müller, N.G., 2010. Keeping Memory Clear and Stable—The Contribution of Human Basal Ganglia and Prefrontal Cortex to Working Memory. J. Neurosci. 30, 9788–9792. doi:10.1523/JNEUROSCI.1513-10.2010

Bai, S., Dokos, S., Ho, K.-A., Loo, C., 2014. A computational modelling study of transcranial direct current stimulation montages used in depression. NeuroImage 87, 332–344. doi:10.1016/j.neuroimage.2013.11.015

Barkley, R.A., 2001. The Inattentive Type of ADHD As a Distinct Disorder: What Remains To Be Done. Clin. Psychol. Sci. Pract. 8, 489–493. doi:10.1093/clipsy.8.4.489

Barkley, R.A., DuPaul, G.J., McMurray, M.B., 1990. Comprehensive evaluation of attention deficit disorder with and without hyperactivity as defined by research criteria. J. Consult. Clin. Psychol. 58, 775–789.

Barry, R.J., Clarke, A.R., Johnstone, S.J., 2003. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. Clin. Neurophysiol. 114, 171–183. doi:10.1016/S1388-2457(02)00362-0

Bastiaansen, M.C., Knösche, T.R., 2000. Tangential derivative mapping of axial MEG applied to event-related desynchronization research. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 111, 1300–1305.

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.-F., Nitsche, M.A., 2013. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J. Physiol. 591, 1987–2000. doi:10.1113/jphysiol.2012.249730

Battaglia, F.P., Benchenane, K., Sirota, A., Pennartz, C.M.A., Wiener, S.I., 2011. The hippocampus: hub of brain network communication for memory. Trends Cogn. Sci. 15, 310–318. doi:10.1016/j.tics.2011.05.008

Bauer, M., Oostenveld, R., Peeters, M., Fries, P., 2006. Tactile spatial attention enhances gamma-band activity in somatosensory cortex and reduces low-frequency activity in parieto-occipital areas. J. Neurosci. Off. J. Soc. Neurosci. 26, 490–501. doi:10.1523/JNEUROSCI.5228-04.2006

Bengson, J.J., Mangun, G.R., Mazaheri, A., 2012. The neural markers of an imminent failure of response inhibition. NeuroImage 59, 1534–1539. doi:10.1016/j.neuroimage.2011.08.034

Berger, P.D.H., 1929. Über das Elektrenkephalogramm des Menschen. Arch. Für Psychiatr. Nervenkrankh. 87, 527–570. doi:10.1007/BF01797193

Bewernick, B.H., Kayser, S., Sturm, V., Schlaepfer, T.E., 2012. Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol. 37, 1975–1985. doi:10.1038/npp.2012.44

Bijsterbosch, J.D., Barker, A.T., Lee, K.-H., Woodruff, P.W.R., 2012. Where does transcranial magnetic stimulation (TMS) stimulate? Modelling of induced field maps for some common cortical and cerebellar targets. Med. Biol. Eng. Comput. 50, 671–681. doi:10.1007/s11517-012-0922-8

Birbaumer, N., Cohen, L.G., 2007. Brain-computer interfaces: communication and restoration of movement in paralysis. J. Physiol. 579, 621–636. doi:10.1113/jphysiol.2006.125633

Blomstedt, P., Sjöberg, R.L., Hansson, M., Bodlund, O., Hariz, M.I., 2011. Deep brain stimulation in the treatment of depression. Acta Psychiatr. Scand. 123, 4–11. doi:10.1111/j.1600-0447.2010.01625.x

Boehnke, S.E., Munoz, D.P., 2008. On the importance of the transient visual response in the superior colliculus. Curr. Opin. Neurobiol. 18, 544–551. doi:10.1016/j.conb.2008.11.004

Bollimunta, A., Mo, J., Schroeder, C.E., Ding, M., 2011. Neuronal mechanisms and attentional modulation of corticothalamic *α* oscillations. J. Neurosci. Off. J. Soc. Neurosci. 31, 4935–4943. doi:10.1523/JNEUROSCI.5580-10.2011

Bonnefond, M., Jensen, O., 2012. Alpha oscillations serve to protect working memory maintenance against anticipated distracters. Curr. Biol. CB 22, 1969–1974. doi:10.1016/j.cub.2012.08.029

Bonnefond, M., Jensen, O., 2013. The role of gamma and alpha oscillations for blocking out distraction. Commun. Integr. Biol. 6, e22702. doi:10.4161/cib.22702

Booth, J.E., Carlson, C.L., Tucker, D.M., 2007. Performance on a neurocognitive measure of alerting differentiates ADHD combined and inattentive subtypes: a preliminary report. Arch. Clin. Neuropsychol. Off. J. Natl. Acad. Neuropsychol. 22, 423–432. doi:10.1016/j.acn.2007.01.017

Brainard, D.H., 1997. The Psychophysics Toolbox. Spat. Vis. 10, 433–436.

Brem, A.-K., Fried, P.J., Horvath, J.C., Robertson, E.M., Pascual-Leone, A., 2014. Is neuroenhancement by noninvasive brain stimulation a net zero-sum proposition? NeuroImage, Neuro-enhancement 85, Part 3, 1058–1068. doi:10.1016/j.neuroimage.2013.07.038

Brignani, D., Ruzzoli, M., Mauri, P., Miniussi, C., 2013. Is Transcranial Alternating Current Stimulation Effective in Modulating Brain Oscillations? PLoS ONE 8, e56589. doi:10.1371/journal.pone.0056589

Brockmole, J.R., Logie, R.H., 2013. Age-related change in visual working memory: a study of 55,753 participants aged 8–75. Percept. Sci. 4, 12. doi:10.3389/fpsyg.2013.00012

Buffalo, E.A., Fries, P., Landman, R., Buschman, T.J., Desimone, R., 2011. Laminar differences in gamma and alpha coherence in the ventral stream. Proc. Natl. Acad. Sci. U. S. A. 108, 11262–11267. doi:10.1073/pnas.1011284108

Buzsáki, G., 2006. Rhythms of the Brain. Oxford University Press.

Buzsáki, G., Draguhn, A., 2004. Neuronal oscillations in cortical networks. Science 304, 1926–1929. doi:10.1126/science.1099745

Cabeza, R., Anderson, N.D., Locantore, J.K., McIntosh, A.R., 2002. Aging gracefully: compensatory brain activity in high-performing older adults. NeuroImage 17, 1394–1402.

Calhoon, G.G., O'Donnell, P., 2013. Closing the Gate in the Limbic Striatum: Prefrontal Suppression of Hippocampal and Thalamic Inputs. Neuron 78, 181–190. doi:10.1016/j.neuron.2013.01.032

Callaway, E.M., 2004. Feedforward, feedback and inhibitory connections in primate visual cortex. Neural Netw., Vision and Brain 17, 625–632. doi:10.1016/j.neunet.2004.04.004

Canolty, R.T., Edwards, E., Dalal, S.S., Soltani, M., Nagarajan, S.S., Kirsch, H.E., Berger, M.S., Barbaro, N.M., Knight, R.T., 2006. High Gamma Power Is Phase-Locked to Theta Oscillations in Human Neocortex. Science 313, 1626–1628. doi:10.1126/science.1128115

Cantwell, D.P., 1996. Attention Deficit Disorder: A Review of the Past 10 Years. J. Am. Acad. Child Adolesc. Psychiatry 35, 978–987. doi:10.1097/00004583-199608000-00008

Capotosto, P., Babiloni, C., Romani, G.L., Corbetta, M., 2009. Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. J. Neurosci. Off. J. Soc. Neurosci. 29, 5863–5872. doi:10.1523/JNEUROSCI.0539-09.2009

Capotosto, P., Babiloni, C., Romani, G.L., Corbetta, M., 2012a. Differential contribution of right and left parietal cortex to the control of spatial attention: a simultaneous EEG-rTMS study. Cereb. Cortex N. Y. N 1991 22, 446–454. doi:10.1093/cercor/bhr127

Capotosto, P., Corbetta, M., Romani, G.L., Babiloni, C., 2012b. Electrophysiological correlates of stimulus-driven reorienting deficits after interference with right parietal cortex during a spatial attention task: a TMS-EEG study. J. Cogn. Neurosci. 24, 2363–2371. doi:10.1162/jocn_a_00287

Carr, L., Henderson, J., Nigg, J.T., 2010. Cognitive Control and Attentional Selection in Adolescents with ADHD versus ADD. J. Clin. Child Adolesc. Psychol. Off. J. Soc. Clin. Child Adolesc. Psychol. Am. Psychol. Assoc. Div. 53 39, 726–740. doi:10.1080/15374416.2010.517168

Cavanagh, J.F., Frank, M.J., Klein, T.J., Allen, J.J.B., 2010. Frontal theta links prediction errors to behavioral adaptation in reinforcement learning. NeuroImage 49, 3198–3209. doi:10.1016/j.neuroimage.2009.11.080

Chanes, L., Quentin, R., Tallon-Baudry, C., Valero-Cabré, A., 2013. Causal Frequency-Specific Contributions of Frontal Spatiotemporal Patterns Induced by Non-Invasive Neurostimulation to Human Visual Performance. J. Neurosci. 33, 5000–5005. doi:10.1523/JNEUROSCI.4401-12.2013

Chang, Z., Lichtenstein, P., Larsson, H., 2012. The effects of childhood ADHD symptoms on early-onset substance use: a Swedish twin study. J. Abnorm. Child Psychol. 40, 425–435. doi:10.1007/s10802-011-9575-6

Coffman, B.A., Clark, V.P., Parasuraman, R., 2014. Battery powered thought: Enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. NeuroImage, Neuroenhancement 85, Part 3, 895–908. doi:10.1016/j.neuroimage.2013.07.083

Cohen, J.E., 2005. Human population grows up. Sci. Am. 293, 48–55.

Cohen, M.X., Axmacher, N., Lenartz, D., Elger, C.E., Sturm, V., Schlaepfer, T.E., 2008a. Good Vibrations: Cross-frequency Coupling in the Human Nucleus Accumbens during Reward Processing. J. Cogn. Neurosci. 21, 875–889. doi:10.1162/jocn.2009.21062

Cohen, M.X., Axmacher, N., Lenartz, D., Elger, C.E., Sturm, V., Schlaepfer, T.E., 2008b. Neuroelectric Signatures of Reward Learning and Decision-Making in the Human Nucleus Accumbens. Neuropsychopharmacology 34, 1649–1658. doi:10.1038/npp.2008.222

Cohen, M.X., Axmacher, N., Lenartz, D., Elger, C.E., Sturm, V., Schlaepfer, T.E., 2009. Nuclei Accumbens Phase Synchrony Predicts Decision-Making Reversals Following Negative Feedback. J. Neurosci. 29, 7591–7598. doi:10.1523/JNEUROSCI.5335-08.2009

Cohen, M.X., Bour, L., Mantione, M., Figee, M., Vink, M., Tijssen, M.A.J., van Rootselaar, A.-F., van den Munckhof, P., Schuurman, P.R., Denys, D., 2012. Top-down-directed synchrony from medial frontal cortex to nucleus accumbens during reward anticipation. Hum. Brain Mapp. 33, 246–252. doi:10.1002/hbm.21195

Comoli, E., Coizet, V., Boyes, J., Bolam, J.P., Canteras, N.S., Quirk, R.H., Overton, P.G., Redgrave, P., 2003. A direct projection from superior colliculus to substantia nigra for detecting salient visual events. Nat. Neurosci. 6, 974–980. doi:10.1038/nn1113

Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron 58, 306–324. doi:10.1016/j.neuron.2008.04.017

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201–215. doi:10.1038/nrn755

Dahlén, M., Rosengren, S., 2005. Brands affect slogans affect brands? Competitive interference, brand equity and the brand-slogan link. J. Brand Manag. 12, 151–164. doi:10.1057/palgrave.bm.2540212

Dahlin, E., Neely, A.S., Larsson, A., Bäckman, L., Nyberg, L., 2008. Transfer of Learning After Updating Training Mediated by the Striatum. Science 320, 1510–1512. doi:10.1126/science.1155466

Dayan, E., Censor, N., Buch, E.R., Sandrini, M., Cohen, L.G., 2013. Noninvasive brain stimulation: from physiology to network dynamics and back. Nat. Neurosci. 16, 838–844. doi:10.1038/nn.3422

Deary, I.J., Corley, J., Gow, A.J., Harris, S.E., Houlihan, L.M., Marioni, R.E., Penke, L., Rafnsson, S.B., Starr, J.M., 2009. Age-associated cognitive decline. Br. Med. Bull. 92, 135–152. doi:10.1093/bmb/ldp033

De Graaf, T.A., Gross, J., Paterson, G., Rusch, T., Sack, A.T., Thut, G., 2013. Alpha-Band Rhythms in Visual Task Performance: Phase-Locking by Rhythmic Sensory Stimulation. PLoS ONE 8, e60035. doi:10.1371/journal.pone.0060035

Denys, D., Mantione, M., Figee, M., van den Munckhof, P., Koerselman, F., Westenberg, H., Bosch, A., Schuurman, R., 2010. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. Arch. Gen. Psychiatry 67, 1061–1068. doi:10.1001/archgenpsychiatry.2010.122

Derefinko, K.J., Adams, Z.W., Milich, R., Fillmore, M.T., Lorch, E.P., Lynam, D.R., 2008. Response style differences in the inattentive and combined subtypes of attention-deficit/hyperactivity disorder. J. Abnorm. Child Psychol. 36, 745–758. doi:10.1007/s10802-007-9207-3

Desimone, R., Duncan, J., 1995. Neural mechanisms of selective visual attention. Annu. Rev. Neurosci. 18, 193–222. doi:10.1146/annurev.ne.18.030195.001205

Dhamala, M., Rangarajan, G., Ding, M., 2008a. Analyzing information flow in brain networks with nonparametric Granger causality. NeuroImage 41, 354–362. doi:10.1016/j.neuroimage.2008.02.020

Dhamala, M., Rangarajan, G., Ding, M., 2008b. Estimating Granger causality from fourier and wavelet transforms of time series data. Phys. Rev. Lett. 100, 018701.

Dickhaus, T., Sannelli, C., Müller, K.-R., Curio, G., Blankertz, B., 2009. Predicting BCI performance to study BCI illiteracy. BMC Neurosci. 10, P84. doi:10.1186/1471-2202-10-S1-P84

Ding, M., Chen, Y., Bressler, S.L., 2006. Granger Causality: Basic Theory and Application to Neuroscience, in: Schelter, B., Winterhalder, M., Timmer, J. (Eds.), Handbook of Time Series Analysis. Wiley-VCH Verlag GmbH & Co. KGaA, pp. 437–460.

Doppelmayr, M., Klimesch, W., Pachinger, T., Ripper, B., 1998. Individual differences in brain dynamics: important implications for the calculation of event-related band power. Biol. Cybern. 79, 49–57.

Dorais, A., Sagi, D., 1997. Contrast masking effects change with practice. Vision Res. 37, 1725–1733.

Dosher, B.A., Lu, Z.-L., 2005. Perceptual learning in clear displays optimizes perceptual expertise: learning the limiting process. Proc. Natl. Acad. Sci. U. S. A. 102, 5286–5290. doi:10.1073/pnas.0500492102

Dunnett, C.W., 1955. A Multiple Comparison Procedure for Comparing Several Treatments with a Control. J. Am. Stat. Assoc. 50, 1096–1121. doi:10.2307/2281208

Dustman, R.E., Shearer, D.E., Emmerson, R.Y., 1993. EEG and event-related potentials in normal aging. Prog. Neurobiol. 41, 369–401. doi:10.1016/0301-0082(93)90005-D

Engel, A.K., Fries, P., Singer, W., 2001. Dynamic predictions: oscillations and synchrony in top-down processing. Nat. Rev. Neurosci. 2, 704–716. doi:10.1038/35094565

Engel, A.K., Singer, W., 2001. Temporal binding and the neural correlates of sensory awareness. Trends Cogn. Sci. 5, 16–25.

Enriquez-Geppert, S., Huster, R.J., Scharfenort, R., Mokom, Z.N., Zimmermann, J., Herrmann, C.S., 2014. Modulation of frontal-midline theta by neurofeedback. Biol. Psychol., SAN (Society of Applied Neuroscience) Special issue on Neurofeedback 95, 59–69. doi:10.1016/j.biopsycho.2013.02.019

Ergenoglu, T., Demiralp, T., Bayraktaroglu, Z., Ergen, M., Beydagi, H., Uresin, Y., 2004. Alpha rhythm of the EEG modulates visual detection performance in humans. Brain Res. Cogn. Brain Res. 20, 376–383. doi:10.1016/j.cogbrainres.2004.03.009

Fabiani, M., Low, K.A., Wee, E., Sable, J.J., Gratton, G., 2006. Reduced suppression or labile memory? Mechanisms of inefficient filtering of irrelevant information in older adults. J. Cogn. Neurosci. 18, 637–650. doi:10.1162/jocn.2006.18.4.637

Fallon, S.J., Cools, R., 2014. Reward Acts on the pFC to Enhance Distractor Resistance of Working Memory Representations. J. Cogn. Neurosci. 1–15. doi:10.1162/jocn_a_00676

Farwell, L.A., Donchin, E., 1988. Talking off the top of your head: toward a mental prosthesis utilizing event-related brain potentials. Electroencephalogr. Clin. Neurophysiol. 70, 510–523. doi:10.1016/0013-4694(88)90149-6

Felleman, D.J., Essen, D.C.V., 1991. Distributed Hierarchical Processing in the Primate. Cereb. Cortex 1, 1–47. doi:10.1093/cercor/1.1.1

Fell, J., Ludowig, E., Staresina, B.P., Wagner, T., Kranz, T., Elger, C.E., Axmacher, N., 2011. Medial temporal theta/alpha power enhancement precedes successful memory encoding: evidence based on intracranial EEG. J. Neurosci. Off. J. Soc. Neurosci. 31, 5392–5397. doi:10.1523/JNEUROSCI.3668-10.2011

Figee, M., Luigjes, J., Smolders, R., Valencia-Alfonso, C.-E., van Wingen, G., de Kwaasteniet, B., Mantione, M., Ooms, P., de Koning, P., Vulink, N., Levar, N., Droge, L., van den Munckhof, P., Schuurman, P.R., Nederveen, A., van den Brink, W., Mazaheri, A., Vink, M., Denys, D., 2013. Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. Nat. Neurosci. 16, 386–387. doi:10.1038/nn.3344

Folk, C.L., Lincourt, A.E., 1996. The effects of age on guided conjunction search. Exp. Aging Res. 22, 99–118. doi:10.1080/03610739608254000

Foxe, J.J., Snyder, A.C., 2011. The Role of Alpha-Band Brain Oscillations as a Sensory Suppression Mechanism during Selective Attention. Front. Psychol. 2, 154. doi:10.3389/fpsyg.2011.00154

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Essen, D.C.V., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102, 9673–9678. doi:10.1073/pnas.0504136102

Frank, M.J., Claus, E.D., 2006. Anatomy of a decision: striato-orbitofrontal interactions in reinforcement learning, decision making, and reversal. Psychol. Rev. 113, 300–326. doi:10.1037/0033-295X.113.2.300

Frank, M.J., Loughry, B., O'Reilly, R.C., 2001. Interactions between frontal cortex and basal ganglia in working memory: a computational model. Cogn. Affect. Behav. Neurosci. 1, 137–160.

Frank, M.J., Scheres, A., Sherman, S.J., 2007. Understanding decision-making deficits in neurological conditions: insights from models of natural action selection. Philos. Trans. R. Soc. B Biol. Sci. 362, 1641–1654. doi:10.1098/rstb.2007.2058

Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn. Sci. 9, 474–480. doi:10.1016/j.tics.2005.08.011

Fries, P., Reynolds, J.H., Rorie, A.E., Desimone, R., 2001. Modulation of oscillatory neuronal synchronization by selective visual attention. Science 291, 1560–1563. doi:10.1126/science.291.5508.1560

Fründ, I., Busch, N.A., Schadow, J., Körner, U., Herrmann, C.S., 2007. From perception to action: phase-locked gamma oscillations correlate with reaction times in a speeded response task. BMC Neurosci. 8, 27. doi:10.1186/1471-2202-8-27

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J.H., Kaiser, J., 2003. Neurofeedback treatment for attention-deficit/hyperactivity disorder in children: a comparison with methylphenidate. Appl. Psychophysiol. Biofeedback 28, 1–12.

Fu, K.M., Foxe, J.J., Murray, M.M., Higgins, B.A., Javitt, D.C., Schroeder, C.E., 2001. Attention-dependent suppression of distracter visual input can be cross-modally cued as indexed by anticipatory parieto-occipital alpha-band oscillations. Brain Res. Cogn. Brain Res. 12, 145–152.

Gaeta, H., Friedman, D., Ritter, W., Cheng, J., 2001. An event-related potential evaluation of involuntary attentional shifts in young and older adults. Psychol. Aging 16, 55–68.

Gazzaley, A., Clapp, W., Kelley, J., McEvoy, K., Knight, R.T., D'Esposito, M., 2008. Age-related top-down suppression deficit in the early stages of cortical visual memory processing. Proc. Natl. Acad. Sci. 105, 13122–13126. doi:10.1073/pnas.0806074105

Gazzaniga, M.S., 2008. Cognitive Neuroscience: The Biology of the Mind, Auflage: 3rd international student edition. ed. Norton & Company, New York.

Geerligs, L., Maurits, N.M., Renken, R.J., Lorist, M.M., 2014. Reduced specificity of functional connectivity in the aging brain during task performance. Hum. Brain Mapp. 35, 319–330. doi:10.1002/hbm.22175

Geerligs, L., Saliasi, E., Renken, R.J., Maurits, N.M., Lorist, M.M., 2013. Flexible connectivity in the aging brain revealed by task modulations. Hum. Brain Mapp. doi:10.1002/hbm.22437

Gevins, A., Smith, M.E., 2000. Neurophysiological Measures of Working Memory and Individual Differences in Cognitive Ability and Cognitive Style. Cereb. Cortex 10, 829–839. doi:10.1093/cercor/10.9.829

Gevins, A., Smith, M.E., McEvoy, L., Yu, D., 1997. High-resolution EEG mapping of cortical activation related to working memory: effects of task difficulty, type of processing, and practice. Cereb. Cortex N. Y. N 1991 7, 374–385.

Geweke, J.F., 1984. Measures of Conditional Linear Dependence and Feedback Between Time Series. J. Am. Stat. Assoc. 79, 907–915. doi:10.2307/2288723

Gharabaghi, A., Kraus, D., Leao, M.T., Spüler, M., Walter, A., Bogdan, M., Rosenstiel, W., Naros, G., Ziemann, U., 2014. Coupling brain-machine interfaces with cortical stimulation for brain-state dependent stimulation: enhancing motor cortex excitability for neurorehabilitation. Front. Hum. Neurosci. 8, 122. doi:10.3389/fnhum.2014.00122

Ghaziri, J., Tucholka, A., Larue, V., Blanchette-Sylvestre, M., Reyburn, G., Gilbert, G., Lévesque, J., Beauregard, M., 2013. Neurofeedback Training Induces Changes in White and Gray Matter. Clin. EEG Neurosci. 1550059413476031. doi:10.1177/1550059413476031

Giacobbe, P., Mayberg, H.S., Lozano, A.M., 2009. Treatment resistant depression as a failure of brain homeostatic mechanisms: implications for deep brain stimulation. Exp. Neurol. 219, 44–52. doi:10.1016/j.expneurol.2009.04.028

Gitelman, D.R., Nobre, A.C., Parrish, T.B., LaBar, K.S., Kim, Y.-H., Meyer, J.R., Mesulam, M.-M., 1999. A large-scale distributed network for covert spatial attention Further anatomical delineation based on stringent behavioral and cognitive controls. Brain 122, 1093–1106. doi:10.1093/brain/122.6.1093

Goodale, M.A., Milner, A.D., 1992. Separate visual pathways for perception and action. Trends Neurosci. 15, 20–25.

Gould, I.C., Rushworth, M.F., Nobre, A.C., 2011. Indexing the graded allocation of visuospatial attention using anticipatory alpha oscillations. J. Neurophysiol. 105, 1318–1326. doi:10.1152/jn.00653.2010

Grandy, T.H., Werkle-Bergner, M., Chicherio, C., Lövdén, M., Schmiedek, F., Lindenberger, U., 2013. Individual alpha peak frequency is related to latent factors of general cognitive abilities. NeuroImage 79, 10–18. doi:10.1016/j.neuroimage.2013.04.059

Granger, C.W.J., 1969. Investigating Causal Relations by Econometric Models and Cross-spectral Methods. Econometrica 37, 424–438. doi:10.2307/1912791

Gross, J., Kujala, J., Hamalainen, M., Timmermann, L., Schnitzler, A., Salmelin, R., 2001. Dynamic imaging of coherent sources: Studying neural interactions in the human brain. Proc. Natl. Acad. Sci. U. S. A. 98, 694–699. doi:10.1073/pnas.98.2.694

Gross, J., Schmitz, F., Schnitzler, I., Kessler, K., Shapiro, K., Hommel, B., Schnitzler, A., 2004. Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. Proc. Natl. Acad. Sci. U. S. A. 101, 13050–13055. doi:10.1073/pnas.0404944101

Groth, K.E., Allen, P.A., 2000. Visual attention and aging. Front. Biosci. J. Virtual Libr. 5, D284–297.

Grubert, C., Hurlemann, R., Bewernick, B.H., Kayser, S., Hadrysiewicz, B., Axmacher, N., Sturm, V., Schlaepfer, T.E., 2011. Neuropsychological safety of nucleus accumbens deep brain stimulation for major depression: effects of 12-month stimulation. World J. Biol. Psychiatry Off. J. World Fed. Soc. Biol. Psychiatry 12, 516–527. doi:10.3109/15622975.2011.583940

Gruzelier, J.H., 2013. EEG-neurofeedback for optimising performance. I: A review of cognitive and affective outcome in healthy participants. Neurosci. Biobehav. Rev. doi:10.1016/j.neubiorev.2013.09.015

Guger, C., Ramoser, H., Pfurtscheller, G., 2000. Real-time EEG analysis with subject-specific spatial patterns for a brain-computer interface (BCI). IEEE Trans. Rehabil. Eng. 8, 447–456. doi:10.1109/86.895947

Haber, S.N., 2003. The primate basal ganglia: parallel and integrative networks. J. Chem. Neuroanat., Special Issue on the Human Brain - The Structural Basis for understanding Human Brain function and dysfunction 26, 317–330. doi:10.1016/j.jchemneu.2003.10.003

Haber, S.N., Calzavara, R., 2009. The cortico-basal ganglia integrative network: The role of the thalamus. Brain Res. Bull., Movement Disorders: Focus on the thalamus and basal ganglia 78, 69–74. doi:10.1016/j.brainresbull.2008.09.013

Haber, S.N., Kunishio, K., Mizobuchi, M., Lynd-Balta, E., 1995. The orbital and medial prefrontal circuit through the primate basal ganglia. J. Neurosci. Off. J. Soc. Neurosci. 15, 4851–4867.

Haegens, S., Händel, B.F., Jensen, O., 2011a. Top-down controlled alpha band activity in somatosensory areas determines behavioral performance in a discrimination task. J. Neurosci. Off. J. Soc. Neurosci. 31, 5197–5204. doi:10.1523/JNEUROSCI.5199-10.2011

Haegens, S., Luther, L., Jensen, O., 2012. Somatosensory anticipatory alpha activity increases to suppress distracting input. J. Cogn. Neurosci. 24, 677–685. doi:10.1162/jocn_a_00164

Haegens, S., Nácher, V., Luna, R., Romo, R., Jensen, O., 2011b. α-Oscillations in the monkey sensorimotor network influence discrimination performance by rhythmical inhibition of neuronal spiking. Proc. Natl. Acad. Sci. U. S. A. 108, 19377–19382. doi:10.1073/pnas.1117190108

Haegens, S., Osipova, D., Oostenveld, R., Jensen, O., 2010. Somatosensory working memory performance in humans depends on both engagement and disengagement of regions in a distributed network. Hum. Brain Mapp. 31, 26–35. doi:10.1002/hbm.20842

Halperin, J.M., Healey, D.M., 2011. The influences of environmental enrichment, cognitive enhancement, and physical exercise on brain development: Can we alter the developmental trajectory of ADHD? Neurosci. Biobehav. Rev. 35, 621–634. doi:10.1016/j.neubiorev.2010.07.006

Hamidi, M., Slagter, H.A., Tononi, G., Postle, B.R., Hamidi, M., Slagter, H.A., Tononi, G., Postle, B.R., 2009. Repetitive transcranial magnetic stimulation affects behavior by biasing endogenous cortical oscillations. Front. Integr. Neurosci. 3, 14. doi:10.3389/neuro.07.014.2009

Händel, B.F., Haarmeier, T., Jensen, O., 2011. Alpha oscillations correlate with the successful inhibition of unattended stimuli. J. Cogn. Neurosci. 23, 2494–2502. doi:10.1162/jocn.2010.21557

Hanslmayr, S., Aslan, A., Staudigl, T., Klimesch, W., Herrmann, C.S., Bäuml, K.-H., 2007. Prestimulus oscillations predict visual perception performance between and within subjects. NeuroImage 37, 1465–1473. doi:10.1016/j.neuroimage.2007.07.011

Hanslmayr, S., Klimesch, W., Sauseng, P., Gruber, W., Doppelmayr, M., Freunberger, R., Pecherstorfer, T., 2005a. Visual discrimination performance is related to decreased alpha amplitude but increased phase locking. Neurosci. Lett. 375, 64–68. doi:10.1016/j.neulet.2004.10.092

Hanslmayr, S., Sauseng, P., Doppelmayr, M., Schabus, M., Klimesch, W., 2005b. Increasing individual upper alpha power by neurofeedback improves cognitive performance in human subjects. Appl. Psychophysiol. Biofeedback 30, 1–10.

Hanslmayr, S., Staudigl, T., 2014. How brain oscillations form memories--a processing based perspective on oscillatory subsequent memory effects. NeuroImage 85 Pt 2, 648–655. doi:10.1016/j.neuroimage.2013.05.121

Hanslmayr, S., Staudigl, T., Fellner, M.-C., 2012. Oscillatory power decreases and long-term memory: the information via desynchronization hypothesis. Front. Hum. Neurosci. 6, 74. doi:10.3389/fnhum.2012.00074

Hartmann, T., Schulz, H., Weisz, N., 2011. Probing of Brain States in Real-Time: Introducing the ConSole Environment. Front. Psychol. 2, 36. doi:10.3389/fpsyg.2011.00036

Hazy, T.E., Frank, M.J., O'Reilly, R.C., 2007. Towards an executive without a homunculus: computational models of the prefrontal cortex/basal ganglia system. Philos. Trans. R. Soc. B Biol. Sci. 362, 1601–1613. doi:10.1098/rstb.2007.2055

Heilman, K.M., Van Den Abell, T., 1980. Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention (neglect). Neurology 30, 327–330.

Helfrich, R.F., Schneider, T.R., Rach, S., Trautmann-Lengsfeld, S.A., Engel, A.K., Herrmann, C.S., 2014. Entrainment of brain oscillations by transcranial alternating current stimulation. Curr. Biol. CB 24, 333–339. doi:10.1016/j.cub.2013.12.041

Herrmann, C.S., Rach, S., Neuling, T., Strüber, D., 2013. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front. Hum. Neurosci. 7, 279. doi:10.3389/fnhum.2013.00279

Hikosaka, O., Takikawa, Y., Kawagoe, R., 2000. Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol. Rev. 80, 953–978.

Hogan, M., Collins, P., Keane, M., Kilmartin, L., Kaiser, J., Kenney, J., Lai, R., Upton, N., 2011. Electroencephalographic coherence, aging, and memory: distinct responses to background context and stimulus repetition in younger, older, and older declined groups. Exp. Brain Res. 212, 241–255. doi:10.1007/s00221-011-2726-8

Hoogenboom, N., Schoffelen, J.-M., Oostenveld, R., Parkes, L.M., Fries, P., 2006. Localizing human visual gamma-band activity in frequency, time and space. NeuroImage 29, 764–773. doi:10.1016/j.neuroimage.2005.08.043

Horvath, J.C., Carter, O., Forte, J.D., 2014. Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be). Front. Syst. Neurosci. 8, 2. doi:10.3389/fnsys.2014.00002

Howard, M.W., Rizzuto, D.S., Caplan, J.B., Madsen, J.R., Lisman, J., Aschenbrenner-Scheibe, R., Schulze-Bonhage, A., Kahana, M.J., 2003. Gamma Oscillations Correlate with Working Memory Load in Humans. Cereb. Cortex 13, 1369–1374. doi:10.1093/cercor/bhg084

Huang, Y.-Z., Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2005. Theta Burst Stimulation of the Human Motor Cortex. Neuron 45, 201–206. doi:10.1016/j.neuron.2004.12.033

Huff, W., Lenartz, D., Schormann, M., Lee, S.-H., Kuhn, J., Koulousakis, A., Mai, J., Daumann, J., Maarouf, M., Klosterkötter, J., Sturm, V., 2010. Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: Outcomes after one year. Clin. Neurol. Neurosurg. 112, 137–143. doi:10.1016/j.clineuro.2009.11.006

Hugenschmidt, C.E., Mozolic, J.L., Laurienti, P.J., 2009a. Suppression of multisensory integration by modality-specific attention in aging. Neuroreport 20, 349–353. doi:10.1097/WNR.0b013e328323ab07

Hugenschmidt, C.E., Peiffer, A.M., McCoy, T.P., Hayasaka, S., Laurienti, P.J., 2009b. Preservation of crossmodal selective attention in healthy aging. Exp. Brain Res. 198, 273–285.doi:10.1007/s00221-009-1816-3

Huggins, J.E., Guger, C., Allison, B., Anderson, C.W., Batista, A., Brouwer, A.-M., Brunner, C., Chavarriaga, R., Fried-Oken, M., Gunduz, A., Gupta, D., Kübler, A., Leeb, R., Lotte, F., Miller, L.E., Müller-Putz, G., Rutkowski, T., Tangermann, M., Thompson, D.E., 2014. Workshops of the Fifth International Brain-Computer Interface Meeting: Defining the Future. Brain-Comput. Interfaces 1, 27–49. doi:10.1080/2326263X.2013.876724

Huijbers, W., Pennartz, C.M., Cabeza, R., Daselaar, S.M., 2009. When Learning and Remembering Compete: A Functional MRI Study. PLoS Biol 7, e1000011. doi:10.1371/journal.pbio.1000011

Hursh, J.B., 1939. Conduction Velocity and Diameter of Nerve Fibers. Am. J. Physiol. -- Leg. Content 127, 131–139.

Iuculano, T., Cohen Kadosh, R., 2013. The mental cost of cognitive enhancement. J. Neurosci. Off. J. Soc. Neurosci. 33, 4482–4486. doi:10.1523/JNEUROSCI.4927-12.2013

Jaegle, A., Ro, T., 2014. Direct control of visual perception with phase-specific modulation of posterior parietal cortex. J. Cogn. Neurosci. 26, 422–432. doi:10.1162/jocn_a_00494

Janssen, A.M., Rampersad, S.M., Lucka, F., Lanfer, B., Lew, S., Aydin, U., Wolters, C.H., Stegeman, D.F., Oostendorp, T.F., 2013. The influence of sulcus width on simulated electric fields induced by transcranial magnetic stimulation. Phys. Med. Biol. 58, 4881–4896. doi:10.1088/0031-9155/58/14/4881

Jaušovec, N., Jaušovec, K., 2014. Increasing working memory capacity with theta transcranial alternating current stimulation (tACS). Biol. Psychol. 96, 42–47. doi:10.1016/j.biopsycho.2013.11.006

Jaušovec, N., Jaušovec, K., Pahor, A., 2014. The influence of theta transcranial alternating current stimulation (tACS) on working memory storage and processing functions. Acta Psychol. (Amst.) 146, 1–6. doi:10.1016/j.actpsy.2013.11.011

Jensen, O., Bahramisharif, A., Oostenveld, R., Klanke, S., Hadjipapas, A., Okazaki, Y.O., van Gerven, M.A.J., 2011. Using brain-computer interfaces and brain-state dependent stimulation as tools in cognitive neuroscience. Front. Psychol. 2, 100. doi:10.3389/fpsyg.2011.00100

Jensen, O., Bonnefond, M., VanRullen, R., 2012. An oscillatory mechanism for prioritizing salient unattended stimuli. Trends Cogn. Sci. 16, 200–206. doi:10.1016/j.tics.2012.03.002

Jensen, O., Gelfand, J., Kounios, J., Lisman, J.E., 2002. Oscillations in the alpha band (9-12 Hz) increase with memory load during retention in a short-term memory task. Cereb. Cortex N. Y. N 1991 12, 877–882.

Jensen, O., Kaiser, J., Lachaux, J.-P., 2007. Human gamma-frequency oscillations associated with attention and memory. Trends Neurosci. 30, 317–324. doi:10.1016/j.tins.2007.05.001

Jensen, O., Lisman, J.E., 1996. Novel lists of 7 +/- 2 known items can be reliably stored in an oscillatory short-term memory network: interaction with long-term memory. Learn. Mem. Cold Spring Harb. N 3, 257–263.

Jensen, O., Lisman, J.E., 1998. An oscillatory short-term memory buffer model can account for data on the Sternberg task. J. Neurosci. Off. J. Soc. Neurosci. 18, 10688–10699.

Jensen, O., Mazaheri, A., 2010. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. Front. Hum. Neurosci. 4, 186. doi:10.3389/fnhum.2010.00186

Jensen, O., Tesche, C.D., 2002. Frontal theta activity in humans increases with memory load in a working memory task. Eur. J. Neurosci. 15, 1395–1399.

Jokeit, H., Makeig, S., 1994. Different event-related patterns of gamma-band power in brain waves of fast- and slow-reacting subjects. Proc. Natl. Acad. Sci. U. S. A. 91, 6339–6343.

Jokisch, D., Jensen, O., 2007. Modulation of Gamma and Alpha Activity during a Working Memory Task Engaging the Dorsal or Ventral Stream. J. Neurosci. 27, 3244–3251. doi:10.1523/JNEUROSCI.5399-06.2007

Kahana, M.J., Seelig, D., Madsen, J.R., 2001. Theta returns. Curr. Opin. Neurobiol. 11, 739–744.

Kamiński, J., Brzezicka, A., Wróbel, A., 2011. Short-term memory capacity (7 ± 2) predicted by theta to gamma cycle length ratio. Neurobiol. Learn. Mem. 95, 19–23. doi:10.1016/j.nlm.2010.10.001

Kanayama, N., Tamè, L., Ohira, H., Pavani, F., 2012. Top down influence on visuo-tactile interaction modulates neural oscillatory responses. NeuroImage 59, 3406–3417. doi:10.1016/j.neuroimage.2011.11.076

Kane, M.J., Engle, R.W., 2002. The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. Psychon. Bull. Rev. 9, 637–671. doi:10.3758/BF03196323

Karch, S., Segmiller, F., Hantschk, I., Cerovecki, A., Opgen-Rhein, M., Hock, B., Dargel, S., Leicht, G., Hennig-Fast, K., Riedel, M., Pogarell, O., 2012. Increased gamma oscillations during voluntary selection processes in adult patients with attention deficit/hyperactivity disorder. J. Psychiatr. Res. 46, 1515–1523. doi:10.1016/j.jpsychires.2012.07.017

Kastner, S., De Weerd, P., Desimone, R., Ungerleider, L.G., 1998. Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. Science 282, 108–111.

Kastner, S., Ungerleider, L.G., 2000. Mechanisms of visual attention in the human cortex. Annu. Rev. Neurosci. 23, 315–341. doi:10.1146/annurev.neuro.23.1.315

Keizer, A.W., Verschoor, M., Verment, R.S., Hommel, B., 2010. The effect of gamma enhancing neurofeedback on the control of feature bindings and intelligence measures. Int. J. Psychophysiol. 75, 25–32. doi:10.1016/j.ijpsycho.2009.10.011

Kelly, S.P., Gomez-Ramirez, M., Foxe, J.J., 2009. The strength of anticipatory spatial biasing predicts target discrimination at attended locations: a high-density EEG study. Eur. J. Neurosci. 30, 2224–2234. doi:10.1111/j.1460-9568.2009.06980.x

Kelly, S.P., Lalor, E.C., Reilly, R.B., Foxe, J.J., 2005. Visual spatial attention tracking using high-density SSVEP data for independent brain-computer communication. IEEE Trans. Neural Syst. Rehabil. Eng. Publ. IEEE Eng. Med. Biol. Soc. 13, 172–178. doi:10.1109/TNSRE.2005.847369

Kelly, S.P., Lalor, E.C., Reilly, R.B., Foxe, J.J., 2006. Increases in alpha oscillatory power reflect an active retinotopic mechanism for distracter suppression during sustained visuospatial attention. J. Neurophysiol. 95, 3844–3851. doi:10.1152/jn.01234.2005

Kidd, P.M., 2000. Attention deficit/hyperactivity disorder (ADHD) in children: rationale for its integrative management. Altern. Med. Rev. J. Clin. Ther. 5, 402–428.

Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. Brain Res. Brain Res. Rev. 29, 169–195.

Klimesch, W., 2012. *α*-band oscillations, attention, and controlled access to stored information. Trends Cogn. Sci. 16, 606–617. doi:10.1016/j.tics.2012.10.007

Klimesch, W., Doppelmayr, M., Pachinger, T., Russegger, H., 1997. Event-related desynchronization in the alpha band and the processing of semantic information. Brain Res. Cogn. Brain Res. 6, 83–94.

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., 1996. Theta band power in the human scalp EEG and the encoding of new information. Neuroreport 7, 1235–1240.

Klimesch, W., Freunberger, R., Sauseng, P., 2010. Oscillatory mechanisms of process binding in memory. Neurosci. Biobehav. Rev. 34, 1002–1014. doi:10.1016/j.neubiorev.2009.10.004

Klimesch, W., Sauseng, P., Gerloff, C., 2003a. Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. Eur. J. Neurosci. 17, 1129–1133.

Klimesch, W., Sauseng, P., Gerloff, C., 2003b. Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. Eur. J. Neurosci. 17, 1129–1133. doi:10.1046/j.1460-9568.2003.02517.x

Klimesch, W., Sauseng, P., Hanslmayr, S., 2007. EEG alpha oscillations: the inhibition-timing hypothesis. Brain Res. Rev. 53, 63–88. doi:10.1016/j.brainresrev.2006.06.003

Klingberg, T., 2010. Training and plasticity of working memory. Trends Cogn. Sci. 14, 317–324. doi:10.1016/j.tics.2010.05.002

Klingberg, T., Forssberg, H., Westerberg, H., 2002. Training of working memory in children with ADHD. J. Clin. Exp. Neuropsychol. 24, 781–791. doi:10.1076/jcen.24.6.781.8395

Kohli, C., Leuthesser, L., Suri, R., 2007. Got slogan? Guidelines for creating effective slogans. Bus. Horiz. 50, 415–422. doi:10.1016/j.bushor.2007.05.002

Kontsevich, L.L., Tyler, C.W., 1999. Bayesian adaptive estimation of psychometric slope and threshold. Vision Res. 39, 2729–2737.

Kopell, N., Kramer, M.A., Malerba, P., Whittington, M.A., 2010. Are different rhythms good for different functions? Front. Hum. Neurosci. 4, 187. doi:10.3389/fnhum.2010.00187

Krause, B., Cohen Kadosh, R., 2014. Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. Front. Syst. Neurosci. 8, 25. doi:10.3389/fnsys.2014.00025

Kray, J., Lindenberger, U., 2000. Adult age differences in task switching. Psychol. Aging 15, 126–147.

Kübler, A., Neumann, N., Wilhelm, B., Hinterberger, T., Birbaumer, N., 2004. Predictability of Brain-Computer Communication. J. Psychophysiol. 18, 121–129. doi:10.1027/0269-8803.18.23.121

Laczó, B., Antal, A., Niebergall, R., Treue, S., Paulus, W., 2012. Transcranial alternating stimulation in a high gamma frequency range applied over V1 improves contrast perception but does not modulate spatial attention. Brain Stimulat. 5, 484–491. doi:10.1016/j.brs.2011.08.008

Lakatos, P., Karmos, G., Mehta, A.D., Ulbert, I., Schroeder, C.E., 2008. Entrainment of neuronal oscillations as a mechanism of attentional selection. Science 320, 110–113. doi:10.1126/science.1154735

Lawrence, V., Houghton, S., Tannock, R., Douglas, G., Durkin, K., Whiting, K., 2002. ADHD outside the laboratory: boys' executive function performance on tasks in videogame play and on a visit to the zoo. J. Abnorm. Child Psychol. 30, 447–462.

Lee, T.G., D'Esposito, M., 2012. The dynamic nature of top-down signals originating from prefrontal cortex: a combined fMRI-TMS study. J. Neurosci. Off. J. Soc. Neurosci. 32, 15458–15466. doi:10.1523/JNEUROSCI.0627-12.2012

Lega, B.C., Kahana, M.J., Jaggi, J., Baltuch, G.H., Zaghloul, K., 2011. Neuronal and oscillatory activity during reward processing in the human ventral striatum. Neuroreport 22, 795–800. doi:10.1097/WNR.0b013e32834b2975

Lenartowicz, A., Delorme, A., Walshaw, P.D., Cho, A.L., Bilder, R.M., McGough, J.J., McCracken, J.T., Makeig, S., Loo, S.K., 2014. Electroencephalography correlates of spatial working memory deficits in attention-deficit/hyperactivity disorder: vigilance, encoding, and maintenance. J. Neurosci. Off. J. Soc. Neurosci. 34, 1171–1182. doi:10.1523/JNEUROSCI.1765-13.2014

Lenz, D., Krauel, K., Schadow, J., Baving, L., Duzel, E., Herrmann, C.S., 2008. Enhanced gamma-band activity in ADHD patients lacks correlation with memory performance found in healthy children. Brain Res., Brain Oscillations in Cognition and Cognitive Disorders 1235, 117–132. doi:10.1016/j.brainres.2008.06.023

Li, R., Polat, U., Makous, W., Bavelier, D., 2009. Enhancing the contrast sensitivity function through action video game training. Nat. Neurosci. 12, 549–551. doi:10.1038/nn.2296

Lisman, J., 2005. The theta/gamma discrete phase code occuring during the hippocampal phase precession may be a more general brain coding scheme. Hippocampus 15, 913–922. doi:10.1002/hipo.20121

Lisman, J., 2010. Working memory: the importance of theta and gamma oscillations. Curr. Biol. CB 20, R490–492. doi:10.1016/j.cub.2010.04.011

Lisman, J.E., Jensen, O., 2013. The θ-γ neural code. Neuron 77, 1002–1016. doi:10.1016/j.neuron.2013.03.007

Lockwood, K.A., Marcotte, A.C., Stern, C., 2001. Differentiation of attention-deficit/hyperactivity disorder subtypes: application of a neuropsychological model of attention. J. Clin. Exp. Neuropsychol. 23, 317–330. doi:10.1076/jcen.23.3.317.1179

Logan, J.M., Sanders, A.L., Snyder, A.Z., Morris, J.C., Buckner, R.L., 2002. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. Neuron 33, 827–840.

Lopes da Silva, F., 1991. Neural mechanisms underlying brain waves: from neural membranes to networks. Electroencephalogr. Clin. Neurophysiol. 79, 81–93.

Lopes da Silva, F., 2013. EEG and MEG: relevance to neuroscience. Neuron 80, 1112–1128. doi:10.1016/j.neuron.2013.10.017

Lopes da Silva, F.H., Storm van Leeuwen, W., 1977. The cortical source of the alpha rhythm. Neurosci. Lett. 6, 237–241. doi:10.1016/0304-3940(77)90024-6

Lopes da Silva, F.H., Vos, J.E., Mooibroek, J., Van Rotterdam, A., 1980. Relative contributions of intracortical and thalamo-cortical processes in the generation of alpha rhythms, revealed by partial coherence analysis. Electroencephalogr. Clin. Neurophysiol. 50, 449–456.

Lotte, F., Congedo, M., Lécuyer, A., Lamarche, F., Arnaldi, B., 2007. A review of classification algorithms for EEG-based brain-computer interfaces. J. Neural Eng. 4, R1–R13. doi:10.1088/1741-2560/4/2/R01

Lubar, J.F., Swartwood, M.O., Swartwood, J.N., O'Donnell, P.H., 1995. Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in T.O.V.A. scores, behavioral ratings, and WISC-R performance. Biofeedback Self-Regul. 20, 83–99.

Luber, B., Lisanby, S.H., 2014. Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). NeuroImage, Neuro-enhancement 85, Part 3, 961–970. doi:10.1016/j.neuroimage.2013.06.007

Luck, S.J., Vogel, E.K., 2013. Visual working memory capacity: from psychophysics and neurobiology to individual differences. Trends Cogn. Sci. 17, 391–400. doi:10.1016/j.tics.2013.06.006

Luigjes, J., van den Brink, W., Feenstra, M., van den Munckhof, P., Schuurman, P.R., Schippers, R., Mazaheri, A., De Vries, T.J., Denys, D., 2012. Deep brain stimulation in addiction: a review of potential brain targets. Mol. Psychiatry 17, 572–583. doi:10.1038/mp.2011.114

Maehara, G., Goryo, K., 2007. Perceptual learning in monocular pattern masking: experiments and explanations by the twin summation gain control model of contrast processing. Percept. Psychophys. 69, 1009–1021.

Maier, A., Adams, G.K., Aura, C., Leopold, D.A., 2010. Distinct superficial and deep laminar domains of activity in the visual cortex during rest and stimulation. Front. Syst. Neurosci. 4. doi:10.3389/fnsys.2010.00031

Manoli, Z., Grossman, N., Samaras, T., 2012. Theoretical investigation of transcranial alternating current stimulation using realistic head model, in: 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). Presented at the 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp. 4156–4159. doi:10.1109/EMBC.2012.6346882

Maris, E., Oostenveld, R., 2007. Nonparametric statistical testing of EEG- and MEG-data. J. Neurosci. Methods 164, 177–190. doi:10.1016/j.jneumeth.2007.03.024

Maris, E., Schoffelen, J.-M., Fries, P., 2007. Nonparametric statistical testing of coherence differences. J. Neurosci. Methods 163, 161–175. doi:10.1016/j.jneumeth.2007.02.011

Mathewson, K.E., Prudhomme, C., Fabiani, M., Beck, D.M., Lleras, A., Gratton, G., 2012. Making Waves in the Stream of Consciousness: Entraining Oscillations in EEG Alpha and Fluctuations in Visual Awareness with Rhythmic Visual Stimulation. J. Cogn. Neurosci. 24, 2321–2333. doi:10.1162/jocn_a_00288

Mazaheri, A., Coffey-Corina, S., Mangun, G.R., Bekker, E.M., Berry, A.S., Corbett, B.A., 2010. Functional Disconnection of Frontal Cortex and Visual Cortex in Attention-Deficit/Hyperactivity Disorder. Biol. Psychiatry, Development of Inhibitory Control in Attention-Deficit/Hyperactivity Disorder 67, 617–623. doi:10.1016/j.biopsych.2009.11.022

Mazaheri, A., Fassbender, C., Coffey-Corina, S., Hartanto, T.A., Schweitzer, J.B., Mangun, G.R., 2013. Differential Oscillatory Electroencephalogram Between Attention-Deficit/Hyperactivity Disorder Subtypes and Typically Developing Adolescents. Biol. Psychiatry. doi:10.1016/j.biopsych.2013.08.023

Mazaheri, A., Nieuwenhuis, I.L.C., van Dijk, H., Jensen, O., 2009. Prestimulus alpha and mu activity predicts failure to inhibit motor responses. Hum. Brain Mapp. 30, 1791–1800. doi:10.1002/hbm.20763

McCracken, C.B., Grace, A.A., 2007. High-Frequency Deep Brain Stimulation of the Nucleus Accumbens Region Suppresses Neuronal Activity and Selectively Modulates Afferent Drive in Rat Orbitofrontal Cortex In Vivo. J. Neurosci. 27, 12601–12610. doi:10.1523/JNEUROSCI.3750-07.2007

McCracken, C.B., Grace, A.A., 2009. Nucleus Accumbens Deep Brain Stimulation Produces Region-Specific Alterations in Local Field Potential Oscillations and Evoked Responses In Vivo. J. Neurosci. 29, 5354–5363. doi:10.1523/JNEUROSCI.0131-09.2009

McEvoy, L.K., Pellouchoud, E., Smith, M.E., Gevins, A., 2001. Neurophysiological signals of working memory in normal aging. Cogn. Brain Res. 11, 363–376. doi:10.1016/S0926-6410(01)00009-X

McFarland, D.J., Sarnacki, W.A., Wolpaw, J.R., 2003. Brain-computer interface (BCI) operation: optimizing information transfer rates. Biol. Psychol. 63, 237–251.

McNab, F., Klingberg, T., 2008. Prefrontal cortex and basal ganglia control access to working memory. Nat. Neurosci. 11, 103–107. doi:10.1038/nn2024

Meeuwissen, E.B., Takashima, A., Fernández, G., Jensen, O., 2011. Increase in posterior alpha activity during rehearsal predicts successful long-term memory formation of word sequences. Hum. Brain Mapp. 32, 2045–2053. doi:10.1002/hbm.21167

Meinzer, M., Antonenko, D., Lindenberg, R., Hetzer, S., Ulm, L., Avirame, K., Flaisch, T., Flöel, A., 2012. Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. J. Neurosci. Off. J. Soc. Neurosci. 32, 1859–1866. doi:10.1523/JNEUROSCI.4812-11.2012

Meinzer, M., Lindenberg, R., Antonenko, D., Flaisch, T., Flöel, A., 2013. Anodal Transcranial Direct Current Stimulation Temporarily Reverses Age-Associated Cognitive Decline and Functional Brain Activity Changes. J. Neurosci. 33, 12470–12478. doi:10.1523/JNEUROSCI.5743-12.2013

Meiron, O., Lavidor, M., 2014. Prefrontal oscillatory stimulation modulates access to cognitive control references in retrospective metacognitive commentary. Clin. Neurophysiol. 125, 77–82. doi:10.1016/j.clinph.2013.06.013

Mesulam, M.M., 1999. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. Philos. Trans. R. Soc.

Lond. B. Biol. Sci. 354, 1325–1346. doi:10.1098/rstb.1999.0482

Middleton, F.A., Strick, P.L., 2000. Basal Ganglia Output and Cognition: Evidence from Anatomical, Behavioral, and Clinical Studies. Brain Cogn. 42, 183–200. doi:10.1006/brcg.1999.1099

Milich, R., Balentine, A.C., Lynam, D.R., 2001. ADHD Combined Type and ADHD Predominantly Inattentive Type Are Distinct and Unrelated Disorders. Clin. Psychol. Sci. Pract. 8, 463–488. doi:10.1093/clipsy.8.4.463

Miltner, W.H., Braun, C., Arnold, M., Witte, H., Taub, E., 1999. Coherence of gamma-band EEG activity as a basis for associative learning. Nature 397, 434–436. doi:10.1038/17126

Mitchell, D.J., McNaughton, N., Flanagan, D., Kirk, I.J., 2008. Frontal-midline theta from the perspective of hippocampal "theta." Prog. Neurobiol. 86, 156–185. doi:10.1016/j.pneurobio.2008.09.005

Mitterer, H., Horschig, J.M., Müsseler, J., Majid, A., 2009. The influence of memory on perception: It's not what things look like, it's what you call them. J. Exp. Psychol. Learn. Mem. Cogn. 35, 1557–1562. doi:10.1037/a0017019

Mo, J., Schroeder, C.E., Ding, M., 2011. Attentional Modulation of Alpha Oscillations in Macaque Inferotemporal Cortex. J. Neurosci. 31, 878–882. doi:10.1523/JNEUROSCI.5295-10.2011

Montemurro, M.A., Rasch, M.J., Murayama, Y., Logothetis, N.K., Panzeri, S., 2008. Phase-of-firing coding of natural visual stimuli in primary visual cortex. Curr. Biol. CB 18, 375–380. doi:10.1016/j.cub.2008.02.023

Munoz, D.P., Everling, S., 2004. Look away: the anti-saccade task and the voluntary control of eye movement. Nat. Rev. Neurosci. 5, 218–228. doi:10.1038/nrn1345

Murias, M., Swanson, J.M., Srinivasan, R., 2007. Functional connectivity of frontal cortex in healthy and ADHD children reflected in EEG coherence. Cereb. Cortex N. Y. N 1991 17, 1788–1799. doi:10.1093/cercor/bhl089

Nakagawa, T.T., Woolrich, M., Luckhoo, H., Joensson, M., Mohseni, H., Kringelbach, M.L., Jirsa, V., Deco, G., 2014. How delays matter in an oscillatory whole-brain spiking-neuron network model for MEG alpha-rhythms at rest. NeuroImage 87, 383–394. doi:10.1016/j.neuroimage.2013.11.009

Nauczyciel, C., Robic, S., Dondaine, T., Verin, M., Robert, G., Drapier, D., Naudet, F., Millet, B., 2013. The nucleus accumbens: a target for deep brain stimulation in resistant major depressive disorder. J. Mol. Psychiatry 1, 17. doi:10.1186/2049-9256-1-17

Neggers, S.F.W., Diepen, R.M. van, Zandbelt, B.B., Vink, M., Mandl, R.C.W., Gutteling, T.P., 2012. A functional and structural investigation of the human fronto-basal volitional saccade network. PloS One 7, e29517. doi:10.1371/journal.pone.0029517

Neuling, T., Rach, S., Herrmann, C.S., 2013. Orchestrating neuronal networks: sustained after-effects of transcranial alternating current stimulation depend upon brain states. Front. Hum. Neurosci. 7, 161. doi:10.3389/fnhum.2013.00161

Neuling, T., Rach, S., Wagner, S., Wolters, C.H., Herrmann, C.S., 2012. Good vibrations: Oscillatory phase shapes perception. NeuroImage 63, 771–778. doi:10.1016/j.neuroimage.2012.07.024

Niedermeyer, E., Lopes da Silva, F.H., 2005. Electroencephalography: Basic Principles, Clinical Applications, and Related Fields. Lippincott Williams & Wilkins.

Nielson, K.A., Langenecker, S.A., Garavan, H., 2002. Differences in the functional neuroanatomy of inhibitory control across the adult life span. Psychol. Aging 17, 56–71.

Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J. Physiol. 527 Pt 3, 633–639.

Nolte, G., 2003. The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. Phys. Med. Biol. 48, 3637–3652.

Nuffield Councils on Bioethics, 2013. Novel neurotechnologies: intervening in the brain.

Nunez, P.L., 2000. Toward a quantitative description of large-scale neocortical dynamic function and EEG. Behav. Brain Sci. 23, 371–398; discussion 399–437.

Obermaier, B., Neuper, C., Guger, C., Pfurtscheller, G., 2001. Information transfer rate in a five-classes brain-computer interface. IEEE Trans. Neural Syst. Rehabil. Eng. Publ. IEEE Eng. Med. Biol. Soc. 9, 283–288. doi:10.1109/7333.948456

Oh, H., Jagust, W.J., 2013. Frontotemporal network connectivity during memory encoding is increased with aging and disrupted by beta-amyloid. J. Neurosci. Off. J. Soc. Neurosci. 33, 18425–18437. doi:10.1523/JNEUROSCI.2775-13.2013

Okazaki, Y., De Weerd, P., Murakami, I., Jensen, O., 2012. Does functional inhibition by alpha acivity constitute the “bias” in biased competition? Presented at the Society for Neuroscience Annual Meeting.

Onoda, K., Ishihara, M., Yamaguchi, S., 2012. Decreased functional connectivity by aging is associated with cognitive decline. J. Cogn. Neurosci. 24, 2186–2198. doi:10.1162/jocn_a_00269

Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.-M., 2011. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. Comput. Intell. Neurosci. 2011, 156869. doi:10.1155/2011/156869

OpenBCI, n.d. . OpenBCI.

OpenrTMS, n.d.

O’Reilly, R.C., Frank, M.J., 2006. Making working memory work: a computational model of learning in the prefrontal cortex and basal ganglia. Neural Comput. 18, 283–328. doi:10.1162/089976606775093909

Osipova, D., Takashima, A., Oostenveld, R., Fernández, G., Maris, E., Jensen, O., 2006. Theta and gamma oscillations predict encoding and retrieval of declarative memory. J. Neurosci. Off. J. Soc. Neurosci. 26, 7523–7531. doi:10.1523/JNEUROSCI.1948-06.2006

Park, H., Lee, D.S., Kang, E., Kang, H., Hahm, J., Kim, J.S., Chung, C.K., Jensen, O., 2014. Blocking of irrelevant memories by posterior alpha activity boosts memory encoding. Hum. Brain Mapp. doi:10.1002/hbm.22452

Pascual-Leone, A., Bartres-Faz, D., Keenan, J.P., 1999. Transcranial magnetic stimulation: studying the brain-behaviour relationship by induction of “virtual lesions.” Philos. Trans. R. Soc. Lond. B. Biol. Sci. 354, 1229–1238. doi:10.1098/rstb.1999.0476

Pascual-Leone, A., Freitas, C., Oberman, L., Horvath, J.C., Halko, M., Eldaief, M., Bashir, S., Vernet, M., Shafi, M., Westover, B., Vahabzadeh-Hagh, A.M., Rotenberg, A., 2011. Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI. Brain Topogr. 24, 302–315. doi:10.1007/s10548-011-0196-8

Paulus, M.P., Potterat, E.G., Taylor, M.K., Van Orden, K.F., Bauman, J., Momen, N., Padilla, G.A., Swain, J.L., 2009. A neuroscience approach to optimizing brain resources for human performance in extreme environments. Neurosci. Biobehav. Rev. 33, 1080–1088. doi:10.1016/j.neubiorev.2009.05.003

Pelham Jr, W.E., Gnagy, E.M., Greenslade, K.E., Milich, R., 1992. Teacher Ratings of DSM-III-R Symptoms for the Disruptive Behavior Disorders. J. Am. Acad. Child Adolesc. Psychiatry 31, 210–218. doi:10.1097/00004583-199203000-00006

Pelli, D.G., 1997. The VideoToolbox software for visual psychophysics: transforming numbers into movies. Spat. Vis. 10, 437–442.

Percival, D.B., Walden, A.T., 1993. Spectral Analysis for Physical Applications. Cambridge University Press, Cambridge ; New York, NY, USA.

Perrin, F., Pernier, J., Bertrand, O., Echallier, J.F., 1989. Spherical splines for scalp potential and current density mapping. Electroencephalogr. Clin. Neurophysiol. 72, 184–187.

Perry, R.J., Zeki, S., 2000. The neurology of saccades and covert shifts in spatial attention An event-related fMRI study. Brain 123, 2273–2288. doi:10.1093/brain/123.11.2273

Petersen, S.E., Robinson, D.L., Morris, J.D., 1987. Contributions of the pulvinar to visual spatial attention. Neuropsychologia 25, 97–105. doi:10.1016/0028-3932(87)90046-7

Peters, E., Pritzkuleit, R., Beske, F., Katalinic, A., 2010. [Demographic change and disease rates: a projection until 2050]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 53, 417–426. doi:10.1007/s00103-010-1050-y

Pfurtscheller, G., Lopes da Silva, F.H., 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 110, 1842–1857.

Pfurtscheller, G., Neuper, C., Guger, C., Harkam, W., Ramoser, H., Schlogl, A., Obermaier, B., Pregenzer, M., 2000. Current trends in Graz brain-computer interface (BCI) research. IEEE Trans. Rehabil. Eng. 8, 216–219. doi:10.1109/86.847821

Pierce, R.C., Vassoler, F.M., 2013. Deep brain stimulation for the treatment of addiction: basic and clinical studies and potential mechanisms of action. Psychopharmacology (Berl.) 229, 487–491. doi:10.1007/s00213-013-3214-6

Polanczyk, G., de Lima, M.S., Horta, B.L., Biederman, J., Rohde, L.A., 2007. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am. J. Psychiatry 164, 942–948. doi:10.1176/appi.ajp.164.6.942

Polanía, R., Nitsche, M.A., Korman, C., Batsikadze, G., Paulus, W., 2012a. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr. Biol. CB 22, 1314–1318. doi:10.1016/j.cub.2012.05.021

Polanía, R., Paulus, W., Nitsche, M.A., 2012b. Noninvasively decoding the contents of visual working memory in the human prefrontal cortex within high-gamma oscillatory patterns. J. Cogn. Neurosci. 24, 304–314. doi:10.1162/jocn_a_00151

Poliakoff, E., Ashworth, S., Lowe, C., Spence, C., 2006. Vision and touch in ageing: crossmodal selective attention and visuotactile spatial interactions. Neuropsychologia 44, 507–517. doi:10.1016/j.neuropsychologia.2005.07.004

Posner, M.I., 1980. Orienting of attention. Q. J. Exp. Psychol. 32, 3–25. doi:10.1080/00335558008248231

Pouget, A., Driver, J., 2000. Relating unilateral neglect to the neural coding of space. Curr. Opin. Neurobiol. 10, 242–249.

Priori, A., 2003. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin. Neurophysiol. 114, 589–595. doi:10.1016/S1388-2457(02)00437-6

Raghavachari, S., Kahana, M.J., Rizzuto, D.S., Caplan, J.B., Kirschen, M.P., Bourgeois, B., Madsen, J.R., Lisman, J.E., 2001. Gating of human theta oscillations by a working memory task. J. Neurosci. Off. J. Soc. Neurosci. 21, 3175–3183.

Raghavachari, S., Lisman, J.E., Tully, M., Madsen, J.R., Bromfield, E.B., Kahana, M.J., 2006. Theta Oscillations in Human Cortex During a Working-Memory Task: Evidence for Local Generators. J. Neurophysiol. 95, 1630–1638. doi:10.1152/jn.00409.2005

Ray, S., Maunsell, J.H.R., 2011. Different origins of gamma rhythm and high-gamma activity in macaque visual cortex. PLoS Biol. 9, e1000610. doi:10.1371/journal.pbio.1000610

Reato, D., Rahman, A., Bikson, M., Parra, L.C., 2013. Effects of weak transcranial alternating current stimulation on brain activity—a review of known mechanisms from animal studies. Front. Hum. Neurosci. 7, 687. doi:10.3389/fnhum.2013.00687

Reinhart, R.M.G., Woodman, G.F., 2014. Causal Control of Medial–Frontal Cortex Governs Electrophysiological and Behavioral Indices of Performance Monitoring and Learning. J. Neurosci. 34, 4214–4227. doi:10.1523/JNEUROSCI.5421-13.2014

Reuter-Lorenz, P.A., Jonides, J., Smith, E.E., Hartley, A., Miller, A., Marshuetz, C., Koeppe, R.A., 2000. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J. Cogn. Neurosci. 12, 174–187.

Rihs, T.A., Michel, C.M., Thut, G., 2007. Mechanisms of selective inhibition in visual spatial attention are indexed by alpha-band EEG synchronization. Eur. J. Neurosci. 25, 603–610. doi:10.1111/j.1460-9568.2007.05278.x

Riis, J.L., Chong, H., Ryan, K.K., Wolk, D.A., Rentz, D.M., Holcomb, P.J., Daffner, K.R., 2008. COMPENSATORY NEURAL ACTIVITY DISTINGUISHES DIFFERENT PATTERNS OF NORMAL COGNITIVE AGING. NeuroImage 39, 441–454. doi:10.1016/j.neuroimage.2007.08.034

Rohenkohl, G., Nobre, A.C., 2011. *α* oscillations related to anticipatory attention follow temporal expectations. J. Neurosci. 31, 14076–14084. doi:10.1523/JNEUROSCI.3387-11.2011

Romei, V., Brodbeck, V., Michel, C., Amedi, A., Pascual-Leone, A., Thut, G., 2008. Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. Cereb. Cortex N. Y. N 1991 18, 2010–2018. doi:10.1093/cercor/bhm229

Romei, V., Gross, J., Thut, G., 2010. On the Role of Prestimulus Alpha Rhythms over Occipito-Parietal Areas in Visual Input Regulation: Correlation or Causation? J. Neurosci. 30, 8692–8697. doi:10.1523/JNEUROSCI.0160-10.2010

Romei, V., Gross, J., Thut, G., 2012. Sounds reset rhythms of visual cortex and corresponding human visual perception. Curr. Biol. CB 22, 807–813. doi:10.1016/j.cub.2012.03.025

Rosenberg, J.R., Amjad, A.M., Breeze, P., Brillinger, D.R., Halliday, D.M., 1989. The Fourier approach to the identification of functional coupling between neuronal spike trains. Prog. Biophys. Mol. Biol. 53, 1–31.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin. Neurophysiol. 120, 2008–2039. doi:10.1016/j.clinph.2009.08.016

Ros, T., Munneke, M.A.M., Ruge, D., Gruzelier, J.H., Rothwell, J.C., 2010. Endogenous control of waking brain rhythms induces neuroplasticity in humans. Eur. J. Neurosci. 31, 770–778. doi:10.1111/j.1460-9568.2010.07100.x

Ros, T., Théberge, J., Frewen, P.A., Kluetsch, R., Densmore, M., Calhoun, V.D., Lanius, R.A., 2013. Mind over chatter: Plastic up-regulation of the fMRI salience network directly after EEG neurofeedback. NeuroImage 65, 324–335. doi:10.1016/j.neuroimage.2012.09.046

Roux, F., Uhlhaas, P.J., 2014. Working memory and neural oscillations: alpha-gamma versus theta-gamma codes for distinct WM information? Trends Cogn. Sci. 18, 16–25. doi:10.1016/j.tics.2013.10.010

Rowe, G., Valderrama, S., Hasher, L., Lenartowicz, A., 2006. Attentional disregulation: a benefit for implicit memory. Psychol. Aging 21, 826–830. doi:10.1037/0882-7974.21.4.826

Rubner, Y., Tomasi, C., Guibas, L.J., 1998. A metric for distributions with applications to image databases, in: Sixth International Conference on Computer Vision, 1998. Presented at the Sixth International Conference on Computer Vision, 1998, pp. 59–66. doi:10.1109/ICCV.1998.710701

Ruzon, M.., Tomasi, C., 1999. Color edge detection with the compass operator, in: Computer Vision and Pattern Recognition, 1999. IEEE Computer Society Conference On. Presented at the Computer Vision and Pattern Recognition, 1999. IEEE Computer Society Conference on., p. -166 Vol. 2. doi:10.1109/CVPR.1999.784624

Saalmann, Y.B., Kastner, S., 2011. Cognitive and perceptual functions of the visual thalamus. Neuron 71, 209–223. doi:10.1016/j.neuron.2011.06.027

Saalmann, Y.B., Pinsk, M.A., Wang, L., Li, X., Kastner, S., 2012. The pulvinar regulates information transmission between cortical areas based on attention demands. Science 337, 753–756. doi:10.1126/science.1223082

Sack, A.T., 2009. Parietal cortex and spatial cognition. Behav. Brain Res. 202, 153–161. doi:10.1016/j.bbr.2009.03.012

Safren, S.A., Sprich, S., Mimiaga, M.J., Surman, C., Knouse, L., Groves, M., Otto, M.W., 2010. Cognitive behavioral therapy vs relaxation with educational support for medication-treated adults with adhd and persistent symptoms: A randomized controlled trial. JAMA 304, 875–880. doi:10.1001/jama.2010.1192

Saint-Cyr, J.A., Ungerleider, L.G., Desimone, R., 1990. Organization of visual cortical inputs to the striatum and subsequent outputs to the pallido-nigral complex in the monkey. J. Comp. Neurol. 298, 129–156. doi:10.1002/cne.902980202

Salthouse, T.A., Babcock, R.L., Shaw, R.J., 1991. Effects of adult age on structural and operational capacities in working memory. Psychol. Aging 6, 118–127.

Sampaio-Baptista, C., Khrapitchev, A.A., Foxley, S., Schlagheck, T., Scholz, J., Jbabdi, S., DeLuca, G.C., Miller, K.L., Taylor, A., Thomas, N., Kleim, J., Sibson, N.R., Bannerman, D., Johansen-Berg, H., 2013. Motor Skill Learning Induces Changes in White Matter Microstructure and Myelination. J. Neurosci. 33, 19499–19503. doi:10.1523/JNEUROSCI.3048-13.2013

Sander, M.C., Lindenberger, U., Werkle-Bergner, M., 2012. Lifespan age differences in working memory: A two-component framework. Neurosci. Biobehav. Rev. 36, 2007–2033. doi:10.1016/j.neubiorev.2012.06.004

Sander, M.C., Werkle-Bergner, M., Lindenberger, U., 2012. Amplitude modulations and inter-trial phase stability of alpha-oscillations differentially reflect working memory constraints across the lifespan. NeuroImage 59, 646–654. doi:10.1016/j.neuroimage.2011.06.092

Santarnecchi, E., Polizzotto, N.R., Godone, M., Giovannelli, F., Feurra, M., Matzen, L., Rossi, A., Rossi, S., 2013. Frequency-Dependent Enhancement of Fluid Intelligence Induced by Transcranial Oscillatory Potentials. Curr. Biol. 23, 1449–1453. doi:10.1016/j.cub.2013.06.022

Sauseng, P., Feldheim, J.F., Freunberger, R., Hummel, F.C., 2011. Right Prefrontal TMS Disrupts Interregional Anticipatory EEG Alpha Activity during Shifting of Visuospatial Attention. Front. Psychol. 2, 241. doi:10.3389/fpsyg.2011.00241

Sauseng, P., Griesmayr, B., Freunberger, R., Klimesch, W., 2010. Control mechanisms in working memory: a possible function of EEG theta oscillations. Neurosci. Biobehav. Rev. 34, 1015–1022. doi:10.1016/j.neubiorev.2009.12.006

Sauseng, P., Klimesch, W., 2008. What does phase information of oscillatory brain activity tell us about cognitive processes? Neurosci. Biobehav. Rev. 32, 1001–1013. doi:10.1016/j.neubiorev.2008.03.014

Sauseng, P., Klimesch, W., Gerloff, C., Hummel, F.C., 2009. Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex. Neuropsychologia 47, 284–288. doi:10.1016/j.neuropsychologia.2008.07.021

Sauseng, P., Klimesch, W., Heise, K.F., Gruber, W.R., Holz, E., Karim, A.A., Glennon, M., Gerloff, C., Birbaumer, N., Hummel, F.C., 2009. Brain Oscillatory Substrates of Visual Short-Term Memory Capacity. Curr. Biol. 19, 1846–1852. doi:10.1016/j.cub.2009.08.062

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., Gruber, W.R., Birbaumer, N., 2005. A shift of visual spatial attention is selectively associated with human EEG alpha activity. Eur. J. Neurosci. 22, 2917–2926. doi:10.1111/j.1460-9568.2005.04482.x

Scheeringa, R., Fries, P., Petersson, K.-M., Oostenveld, R., Grothe, I., Norris, D.G., Hagoort, P., Bastiaansen, M.C.M., 2011. Neuronal dynamics underlying high- and low-frequency EEG oscillations contribute independently to the human BOLD signal. Neuron 69, 572–583. doi:10.1016/j.neuron.2010.11.044

Schlaepfer, T.E., Bewernick, B.H., 2013. Deep brain stimulation for major depression. Handb. Clin. Neurol. 116, 235–243. doi:10.1016/B978-0-444-53497-2.00018-8

Schneider, T.R., Debener, S., Oostenveld, R., Engel, A.K., 2008. Enhanced EEG gamma-band activity reflects multisensory semantic matching in visual-to-auditory object priming. NeuroImage 42, 1244–1254. doi:10.1016/j.neuroimage.2008.05.033

Schoffelen, J.-M., Oostenveld, R., Fries, P., 2008. Imaging the human motor system's beta-band synchronization during isometric contraction. NeuroImage 41, 437–447. doi:10.1016/j.neuroimage.2008.01.045

Schroeder, C.E., Lakatos, P., 2009. Low-frequency neuronal oscillations as instruments of sensory selection. Trends Neurosci. 32, 9–18. doi:10.1016/j.tins.2008.09.012

Schutter, D.J.L.G., n.d. Syncing your brain: electric currents to enhance cognition. Trends Cogn. Sci. doi:10.1016/j.tics.2014.02.011

Serruya, M.D., Hatsopoulos, N.G., Paninski, L., Fellows, M.R., Donoghue, J.P., 2002. Instant neural control of a movement signal. Nature 416, 141–142. doi:10.1038/416141a

Shafi, M.M., Brandon Westover, M., Oberman, L., Cash, S.S., Pascual-Leone, A., 2014. Modulation of EEG functional connectivity networks in subjects undergoing repetitive transcranial magnetic stimulation. Brain Topogr. 27, 172–191. doi:10.1007/s10548-013-0277-y

Shibata, K., Watanabe, T., Sasaki, Y., Kawato, M., 2011. Perceptual learning incepted by decoded fMRI neurofeedback without stimulus presentation. Science 334, 1413–1415. doi:10.1126/science.1212003

Silvanto, J., Pascual-Leone, A., 2008. State-dependency of transcranial magnetic stimulation. Brain Topogr. 21, 1–10. doi:10.1007/s10548-008-0067-0

Smolders, R., Mazaheri, A., van Wingen, G., Figee, M., de Koning, P.P., Denys, D., 2013. Deep Brain Stimulation Targeted at the Nucleus Accumbens Decreases the Potential for Pathologic Network Communication. Biol. Psychiatry 74, e27–e28. doi:10.1016/j.biopsych.2013.03.012

Snowball, A., Tachtsidis, I., Popescu, T., Thompson, J., Delazer, M., Zamarian, L., Zhu, T., Cohen Kadosh, R., 2013. Long-term enhancement of brain function and cognition using cognitive training and brain stimulation. Curr. Biol. CB 23, 987–992. doi:10.1016/j.cub.2013.04.045

Sowden, P.T., Rose, D., Davies, I.R.L., 2002. Perceptual learning of luminance contrast detection: specific for spatial frequency and retinal location but not orientation. Vision Res. 42, 1249–1258.

Spaak, E., Bonnefond, M., Maier, A., Leopold, D.A., Jensen, O., 2012. Layer-specific entrainment of gamma-band neural activity by the alpha rhythm in monkey visual cortex. Curr. Biol. CB 22, 2313–2318. doi:10.1016/j.cub.2012.10.020

Spaak, E., Lange, F.P. de, Jensen, O., 2014. Local Entrainment of Alpha Oscillations by Visual Stimuli Causes Cyclic Modulation of Perception. J. Neurosci. 34, 3536–3544. doi:10.1523/JNEUROSCI.4385-13.2014

Spitzer, B., Blankenburg, F., 2012. Supramodal parametric working memory processing in humans. J. Neurosci. Off. J. Soc. Neurosci. 32, 3287–3295. doi:10.1523/JNEUROSCI.5280-11.2012

Staudigl, T., Hanslmayr, S., 2013. Theta oscillations at encoding mediate the context-dependent nature of human episodic memory. Curr. Biol. CB 23, 1101–1106. doi:10.1016/j.cub.2013.04.074

Staufenbiel, S.M., Brouwer, A.-M., Keizer, A.W., van Wouwe, N.C., 2014. Effect of beta and gamma neurofeedback on memory and intelligence in the elderly. Biol. Psychol., SAN (Society of Applied Neuroscience) Special issue on Neurofeedback 95, 74–85. doi:10.1016/j.biopsycho.2013.05.020

Stolk, A., Todorovic, A., Schoffelen, J.-M., Oostenveld, R., 2013. Online and offline tools for head movement compensation in MEG. NeuroImage 68, 39–48. doi:10.1016/j.neuroimage.2012.11.047

Strens, L.H.A., Oliviero, A., Bloem, B.R., Gerschlager, W., Rothwell, J.C., Brown, P., 2002. The effects of subthreshold 1 Hz repetitive TMS on cortico-cortical and interhemispheric coherence. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 113, 1279–1285.

Strenziok, M., Parasuraman, R., Clarke, E., Cisler, D.S., Thompson, J.C., Greenwood, P.M., 2014. Neurocognitive enhancement in older adults: Comparison of three cognitive training tasks to test a hypothesis of training transfer in brain connectivity. NeuroImage, Neuro-enhancement 85, Part 3, 1027–1039. doi:10.1016/j.neuroimage.2013.07.069

Strüber, D., Rach, S., Trautmann-Lengsfeld, S.A., Engel, A.K., Herrmann, C.S., 2014. Antiphasic 40 Hz oscillatory current stimulation affects bistable motion perception. Brain Topogr. 27, 158–171. doi:10.1007/s10548-013-0294-x

Suffczynski, P., Kalitzin, S., Pfurtscheller, G., Lopes da Silva, F.H., 2001. Computational model of thalamo-cortical networks: dynamical control of alpha rhythms in relation to focal attention. Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 43, 25–40.

Sykacek, P., Roberts, S.J., Stokes, M., 2004. Adaptive BCI based on variational Bayesian Kalman filtering: an empirical evaluation. IEEE Trans. Biomed. Eng. 51, 719–727. doi:10.1109/TBME.2004.824128

Tales, A., Troscianko, T., Wilcock, G.K., Newton, P., Butler, S.R., 2002. Age-related changes in the preattentional detection of visual change. Neuroreport 13, 969–972.

Tallon-Baudry, Bertrand, 1999. Oscillatory gamma activity in humans and its role in object representation. Trends Cogn. Sci. 3, 151–162.

Tallon-Baudry, C., Bertrand, O., Delpuech, C., Pernier, J., 1996. Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. J. Neurosci. Off. J. Soc. Neurosci. 16, 4240–4249.

Tallon-Baudry, C., Bertrand, O., Hénaff, M.-A., Isnard, J., Fischer, C., 2005. Attention Modulates Gamma-band Oscillations Differently in the Human Lateral Occipital Cortex and Fusiform Gyrus. Cereb. Cortex 15, 654–662. doi:10.1093/cercor/bhh167

Tallon-Baudry, C., Bertrand, O., Peronnet, F., Pernier, J., 1998. Induced gamma-band activity during the delay of a visual short-term memory task in humans. J. Neurosci. Off. J. Soc. Neurosci. 18, 4244–4254.

Tanskanen, T., Näsänen, R., Montez, T., Päällysaho, J., Hari, R., 2005. Face recognition and cortical responses show similar sensitivity to noise spatial frequency. Cereb. Cortex N. Y. N 1991 15, 526–534. doi:10.1093/cercor/bhh152

Taylor, D.M., Tillery, S.I.H., Schwartz, A.B., 2002. Direct cortical control of 3D neuroprosthetic devices. Science 296, 1829–1832. doi:10.1126/science.1070291

Ter Huurne, N., Onnink, M., Kan, C., Franke, B., Buitelaar, J., Jensen, O., 2013. Behavioral consequences of aberrant alpha lateralization in attention-deficit/hyperactivity disorder. Biol. Psychiatry 74, 227–233. doi:10.1016/j.biopsych.2013.02.001

Thut, G., Miniussi, C., 2009. New insights into rhythmic brain activity from TMS–EEG studies. Trends Cogn. Sci. 13, 182–189. doi:10.1016/j.tics.2009.01.004

Thut, G., Nietzel, A., Brandt, S.A., Pascual-Leone, A., 2006. Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. J. Neurosci. Off. J. Soc. Neurosci. 26, 9494–9502. doi:10.1523/JNEUROSCI.0875-06.2006

Thut, G., Pascual-Leone, A., 2010. A Review of Combined TMS-EEG Studies to Characterize Lasting Effects of Repetitive TMS and Assess Their Usefulness in Cognitive and Clinical Neuroscience. Brain Topogr. 22, 219–232. doi:10.1007/s10548-009-0115-4

Thut, G., Schyns, P.G., Gross, J., 2011a. Entrainment of Perceptually Relevant Brain Oscillations by Non-Invasive Rhythmic Stimulation of the Human Brain. Front. Psychol. 2. doi:10.3389/fpsyg.2011.00170

Thut, G., Veniero, D., Romei, V., Miniussi, C., Schyns, P., Gross, J., 2011b. Rhythmic TMS Causes Local Entrainment of Natural Oscillatory Signatures. Curr. Biol. 21, 1176–1185. doi:10.1016/j.cub.2011.05.049

Tonin, L., Leeb, R., Del R Millán, J., 2012. Time-dependent approach for single trial classification of covert visuospatial attention. J. Neural Eng. 9, 045011. doi:10.1088/1741-2560/9/4/045011

Tonin, L., Leeb, R., Sobolewski, A., Millán, J. del R., 2013. An online EEG BCI based on covert visuospatial attention in absence of exogenous stimulation. J. Neural Eng. 10, 056007. doi:10.1088/1741-2560/10/5/056007

Tort, A.B.L., Kramer, M.A., Thorn, C., Gibson, D.J., Kubota, Y., Graybiel, A.M., Kopell, N.J., 2008. Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. Proc. Natl. Acad. Sci. 105, 20517–20522. doi:10.1073/pnas.0810524105

Treder, M.S., Bahramisharif, A., Schmidt, N.M., van Gerven, M.A.J., Blankertz, B., 2011. Brain-computer interfacing using modulations of alpha activity induced by covert shifts of attention. J. Neuroengineering Rehabil. 8, 24. doi:10.1186/1743-0003-8-24

Valdés-Hernández, P.A., Ojeda-González, A., Martínez-Montes, E., Lage-Castellanos, A., Virués-Alba, T., Valdés-Urrutia, L., Valdes-Sosa, P.A., 2010. White matter architecture rather than cortical surface area correlates with the EEG alpha rhythm. NeuroImage 49, 2328–2339. doi:10.1016/j.neuroimage.2009.10.030

Vallar, G., Perani, D., 1986. The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. Neuropsychologia 24, 609–622.

Van Dijk, H., Schoffelen, J.-M., Oostenveld, R., Jensen, O., 2008. Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. J. Neurosci. Off. J. Soc. Neurosci. 28, 1816–1823. doi:10.1523/JNEUROSCI.1853-07.2008

Van Dongen-Boomsma, M., Vollebregt, M.A., Slaats-Willemse, D., Buitelaar, J.K., 2013. A randomized placebo-controlled trial of electroencephalographic (EEG) neurofeedback in children with attention-deficit/hyperactivity disorder. J. Clin. Psychiatry 74, 821–827. doi:10.4088/JCP.12m08321

Van Ede, F., Köster, M., Maris, E., 2012. Beyond establishing involvement: quantifying the contribution of anticipatory α- and β-band suppression to perceptual improvement with attention. J. Neurophysiol. 108, 2352–2362. doi:10.1152/jn.00347.2012

Van Gerven, M., Bahramisharif, A., Heskes, T., Jensen, O., 2009a. Selecting features for BCI control based on a covert spatial attention paradigm. Neural Netw. Off. J. Int. Neural Netw. Soc. 22, 1271–1277. doi:10.1016/j.neunet.2009.06.004

Van Gerven, M., Farquhar, J., Schaefer, R., Vlek, R., Geuze, J., Nijholt, A., Ramsey, N., Haselager, P., Vuurpijl, L., Gielen, S., Desain, P., 2009b. The brain-computer interface cycle. J. Neural Eng. 6, 041001. doi:10.1088/1741-2560/6/4/041001

Van Gerven, M., Jensen, O., 2009. Attention modulations of posterior alpha as a control signal for two-dimensional brain-computer interfaces. J. Neurosci. Methods 179, 78–84. doi:10.1016/j.jneumeth.2009.01.016

Van Pelt, S., Boomsma, D.I., Fries, P., 2012. Magnetoencephalography in twins reveals a strong genetic determination of the peak frequency of visually induced γ-band synchronization. J. Neurosci. Off. J. Soc. Neurosci. 32, 3388–3392. doi:10.1523/JNEUROSCI.5592-11.2012

Van Pelt, S., Fries, P., 2013. Visual stimulus eccentricity affects human gamma peak frequency. NeuroImage 78, 439–447. doi:10.1016/j.neuroimage.2013.04.040

VanRullen, R., Zoefel, B., Ilhan, B., 2014. On the cyclic nature of perception in vision versus audition. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 369, 20130214. doi:10.1098/rstb.2013.0214

Van Schouwenburg, M.R., den Ouden, H.E.M., Cools, R., 2010. The human basal ganglia modulate frontal-posterior connectivity during attention shifting. J. Neurosci. Off. J. Soc. Neurosci. 30, 9910–9918. doi:10.1523/JNEUROSCI.1111-10.2010

Van Schouwenburg, M.R., den Ouden, H.E.M., Cools, R., 2013. Selective Attentional Enhancement and Inhibition of Fronto-Posterior Connectivity by the Basal Ganglia During Attention Switching. Cereb. Cortex N. Y. N 1991. doi:10.1093/cercor/bht345

Varela, F., Lachaux, J.P., Rodriguez, E., Martinerie, J., 2001. The brainweb: phase synchronization and large-scale integration. Nat. Rev. Neurosci. 2, 229–239. doi:10.1038/35067550

Vaughan, T.M., McFarland, D.J., Schalk, G., Sarnacki, W.A., Krusienski, D.J., Sellers, E.W., Wolpaw, J.R., 2006. The wadsworth BCI research and development program: at home with BCI. IEEE Trans. Neural Syst. Rehabil. Eng. 14, 229–233. doi:10.1109/TNSRE.2006.875577

Veniero, D., Ponzo, V., Koch, G., 2013. Paired associative stimulation enforces the communication between interconnected areas. J. Neurosci. Off. J. Soc. Neurosci. 33, 13773–13783. doi:10.1523/JNEUROSCI.1777-13.2013

Verret, C., Guay, M.-C., Berthiaume, C., Gardiner, P., Béliveau, L., 2012. A Physical Activity Program Improves Behavior and Cognitive Functions in Children With ADHD An Exploratory Study. J. Atten. Disord. 16, 71–80. doi:10.1177/1087054710379735

Vidal-Piñeiro, D., Martin-Trias, P., Arenaza-Urquijo, E.M., Sala-Llonch, R., Clemente, I.C., Mena-Sánchez, I., Bargalló, N., Falcón, C., Pascual-Leone, A., Bartrés-Faz, D., 2014. Task-dependent Activity and Connectivity Predict Episodic Memory Network-based Responses to Brain Stimulation in Healthy Aging. Brain Stimulat. 7, 287–296. doi:10.1016/j.brs.2013.12.016

Vidaurre, C., Blankertz, B., 2010. Towards a Cure for BCI Illiteracy. Brain Topogr. 23, 194–198. doi:10.1007/s10548-009-0121-6

Vollebregt, M.A., van Dongen-Boomsma, M., Buitelaar, J.K., Slaats-Willemse, D., 2013. Does EEG-neurofeedback improve neurocognitive functioning in children with attention-deficit/hyperactivity disorder? A systematic review and a double-blind placebo-controlled study. J. Child Psychol. Psychiatry. doi:10.1111/jcpp.12143

Vollmann, H., Conde, V., Sewerin, S., Taubert, M., Sehm, B., Witte, O.W., Villringer, A., Ragert, P., 2013. Anodal transcranial direct current stimulation (tDCS) over supplementary motor area (SMA) but not pre-SMA promotes short-term visuomotor learning. Brain Stimulat. 6, 101–107. doi:10.1016/j.brs.2012.03.018

Von Stein, A., Sarnthein, J., 2000. Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. Int. J. Psychophysiol. Off. J. Int. Organ. Psychophysiol. 38, 301–313.

Wagner, T., Eden, U., Rushmore, J., Russo, C.J., Dipietro, L., Fregni, F., Simon, S., Rotman, S., Pitskel, N.B., Ramos-Estebanez, C., Pascual-Leone, A., Grodzinsky, A.J., Zahn, M., Valero-Cabré, A., 2014. Impact of brain tissue filtering on neurostimulation fields: A modeling study. NeuroImage, Neuroenhancement 85, Part 3, 1048–1057. doi:10.1016/j.neuroimage.2013.06.079

Wang, J.-R., Hsieh, S., 2013. Neurofeedback training improves attention and working memory performance. Clin. Neurophysiol. 124, 2406–2420. doi:10.1016/j.clinph.2013.05.020

Wang, X.-J., 2010. Neurophysiological and Computational Principles of Cortical Rhythms in Cognition. Physiol. Rev. 90, 1195–1268. doi:10.1152/physrev.00035.2008

Waring, J.D., Addis, D.R., Kensinger, E.A., 2013. Effects of aging on neural connectivity underlying selective memory for emotional scenes. Neurobiol. Aging 34, 451–467. doi:10.1016/j.neurobiolaging.2012.03.011

Wassermann, E.M., 1998. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr. Clin. Neurophysiol. 108, 1–16.

Weiler, M.D., Bernstein, J.H., Bellinger, D., Waber, D.P., 2002. Information processing deficits in children with attention-deficit/hyperactivity disorder, inattentive type, and children with reading disability. J. Learn. Disabil. 35, 448–461.

Weiss, M., Worling, D., Wasdell, M., 2003. A chart review study of the inattentive and combined types of ADHD. J. Atten. Disord. 7, 1–9.

Werkle-Bergner, M., Shing, Y.L., Müller, V., Li, S.-C., Lindenberger, U., 2009. EEG gamma-band synchronization in visual coding from childhood to old age: evidence from evoked power and inter-trial phase locking. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 120, 1291–1302. doi:10.1016/j.clinph.2009.04.012

White, H.A., 2007. Inhibitory control of proactive interference in adults with ADHD. J. Atten. Disord. 11, 141–149. doi:10.1177/1087054706295604

Wiener, N., 1956. The theory of prediction. Modern mathematics for the engineer. McGraw-Hill, New York.

Wilson, G.T., 1972. The Factorization of Matricial Spectral Densities. SIAM J. Appl. Math. 23, 420–426.

Wolpaw, J.R., Birbaumer, N., McFarland, D.J., Pfurtscheller, G., Vaughan, T.M., 2002. Brain-computer interfaces for communication and control. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 113, 767–791.

Wolpaw, J.R., McFarland, D.J., Neat, G.W., Forneris, C.A., 1991. An EEG-based brain-computer interface for cursor control. Electroencephalogr. Clin. Neurophysiol. 78, 252–259. doi:10.1016/0013-4694(91)90040-B

Worden, M.S., Foxe, J.J., Wang, N., Simpson, G.V., 2000. Anticipatory biasing of visuospatial attention indexed by retinotopically specific alpha-band electroencephalography increases over occipital cortex. J. Neurosci. Off. J. Soc. Neurosci. 20, RC63.

Xing, D., Yeh, C.-I., Burns, S., Shapley, R.M., 2012. Laminar analysis of visually evoked activity in the primary visual cortex. Proc. Natl. Acad. Sci. 109, 13871–13876. doi:10.1073/pnas.1201478109

Yamagishi, N., Callan, D.E., Goda, N., Anderson, S.J., Yoshida, Y., Kawato, M., 2003. Attentional modulation of oscillatory activity in human visual cortex. NeuroImage 20, 98–113.

Yang, L., Hasher, L., 2007. The enhanced effects of pictorial distraction in older adults. J. Gerontol. B. Psychol. Sci. Soc. Sci. 62, P230–233.

Yordanova, J., Banaschewski, T., Kolev, V., Woerner, W., Rothenberger, A., 2001. Abnormal early stages of task stimulus processing in children with attention-deficit hyperactivity disorder – evidence from event-related gamma oscillations. Clin. Neurophysiol. 112, 1096–1108. doi:10.1016/S1388-2457(01)00524-7

Zaehle, T., Rach, S., Herrmann, C.S., 2010. Transcranial Alternating Current Stimulation Enhances Individual Alpha Activity in Human EEG. PLoS ONE 5, e13766. doi:10.1371/journal.pone.0013766

Zanto, T.P., Chadick, J.Z., Gazzaley, A., 2014. Anticipatory alpha phase influences visual working memory performance. NeuroImage 85 Pt 2, 794–802. doi:10.1016/j.neuroimage.2013.07.048

Zatorre, R.J., Fields, R.D., Johansen-Berg, H., 2012. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat. Neurosci. 15, 528–536. doi:10.1038/nn.3045

Zoefel, B., Huster, R.J., Herrmann, C.S., 2011. Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. NeuroImage 54, 1427–1431. doi:10.1016/j.neuroimage.2010.08.078

Nederlandse samenvatting

Stel je voor dat je voor een verkeerslicht op het groene licht staat te wachten. Een verkeerslicht (zie figuur 1) is speciaal ontworpen om bottom-up aandachtprocessen te activeren. Een helder licht verandert van locatie en kleur, waardoor je aandacht wordt getrokken in een bottom-up manier. Ondanks de opkomende, duidelijke verandering in je gezichtsveld, richt je jouw aandacht exclusief op het verkeerslicht en negeer je de omgeving. Je zou kunnen besluiten om in plaats van naar het verkeerslicht liever naar de rode Ferrari op de nabijgelegen parkeerplaats te kijken. Echter, als het jouw huidige belangrijkste prioriteit is om jouw bestemming zo snel mogelijk te bereiken, dan kun je beter niet afgeleid worden van het verkeerslicht. Dus negeer je bewust jouw omgeving om je reactietijd te verbeteren wanneer het licht op groen springt. Dit wordt top-down controle van aandacht genoemd. In tegenstelling tot de automatische bottom-up aandachtsprocessen kun je de hoeveelheid top-down aandachtscontrole bewust moduleren.

Figuur 1: Een verkeerslicht, waarop de middenste licht op oranje staat (of geel als je Duits bent, zie Mitterer et al., 2009)

Wordt er visueel-ruimtelijk aandacht aan een bepaalde plek besteedt, dan vinden er saccadische oogbewegingen naar exact deze plek plaats. Op deze manier blijft het centrum van het netvlies, de fovea, gefixeerd op waar je het meest geïnteresseerd in bent: het verkeerslicht. In het daglicht is de ruimtelijke resolutie het hoogst in de fovea, dus is het zinvol om ook te kijken naar waar je het meest geïnteresseerd in bent (zie Gazzaniga, 2008).

In tegenstelling tot deze openlijke visueel-ruimtelijke aandacht, kun je jouw aandacht ook richten op een andere ruimtelijke locatie dan waar je op dit moment naar kijkt. Dit is de zogenaamde geheime visueel-ruimtelijke aandacht, of in het kort, geheime aandacht (Posner, 1980). Bijvoorbeeld, tijdens het wachten op het groene licht, zou jouw levenspartner kunnen beginnen tegen je te praten en zou kunnen vragen om naar zijn gezicht te kijken terwijl jullie praten. Toch zou je in het geheim je aandacht verder kunnen besteden aan het verkeerslicht in plaats van aan je partner, omdat je een snelle reactie op het groene licht belangrijker vindt dan het analyseren van zijn emotionele gelaatsuitdrukkingen.

Het visuele systeem in het menselijk brein is vrij complex. Visuele input komt het eerst aan bij de ogen. Fotoreceptorcellen converteren fotonen uit het inkomende licht in elektrische signalen, die dan verder worden doorgegeven aan de hersenen: visuele informatie wordt via de optische chiasma doorgegeven aan de laterale geniculate nucleus (LGN) in de thalamus en vandaar naar de visuele cortex (zie bijv Gazzaniga , 2008) en naar andere subcorticale gebieden zoals de superior colliculus (zie bv Boehnke en Munoz, 2008). De optische chiasma combineert informatie van beide ogen in een gezichtsveld-specifieke wijze: het linker gezichtsveld van beide ogen word gecombineerd en via de LGN naar de rechter visuele cortex gestuurt en het rechter gezichtsveld van beide ogen wordt gecombineerd en via de LGN verzonden naar de linke visuele cortex. De visuele cortex is de belangrijkste corticale invoerlaag waar visuele informatie wordt verwerkt en verzonden naar hogere visuele gebieden. De visuele cortex ontvangt ook terugkerende verbindingen van hogere visuele gebieden, waardoor visuele informatie geactualiseerd wordt met het resultaat van de verwerking van deze hogere visuele gebieden.

Neuronale oscillaties vertegenwoordigen fundamentele functies van het menselijk brein, waar verschillende frequentiebanden lijken te worden betrokken bij verschillende, deels overlappende processen (Buzsáki en Draguhn, 2004). Dit proefschrift beschrijft voornamelijk alfa-band oscillaties, meestal gedefinieerd als de frequentieband tussen de 8 en 14 Hz. Voor een lange tijd dacht men dat alfa-band oscillaties bedoeld waren om de onbelaste toestand van het menselijk brein te vertegenwoordigen (Adrian en Matthews, 1934; Berger, 1929). De huidige dominante hypothese is dat alfa-band oscillaties een belangrijke functionele rol spelen door het remmen van irrelevante hersengebieden (Foxe en Snyder, 2011; Fu et al, 2001;. Jensen en Mazaheri, 2010; Klimesch, 1999a; Klimesch et al. , 2007). Bijvoorbeeld, tijdens geheime aandacht verwerkt de ipsilaterale occipitopariëtale cortex het onbeheerd gezichtsveld en vertoont een sterke alpha oscillatie. Dit toont een functionele remming van dit taak-irrelevant gebied

aan. In tegenstelling heeft de contralaterale hemisfeer zwakke alpha-oscillaties, waardoor deze hemisfeer functioneel wordt gedisinhibiteerd. Hierdoor kan visuele informatie worden verwerkt. Deze disbalance van de sterkte van ipsi- en contralaterale hemisfeer heet alfa lateralisatie. Een algemeen belangrijk kenmerk van alfa oscillaties is dat ze anticiperend zijn, dit betekent dat deze alpha-band hemisferische lateralisatie al voor het begin van visuele stimulatie ontstaat (Worden et al., 2000). Talrijke studies vonden sterke correlaties tussen de kwaliteit van de verwerking van komende visuele stimulaties en de mate van de alfa-band lateralisatie op dat moment (Kelly et al, 2009;. Thut et al., 2006), wat aangeeft dat posterior alfa-oscillaties betrouwbare neurale correlaten van visueel-ruimtelijke aandacht zijn. De sterktes van de posterieure alfa lateralisatie verschillen ook tussen individuen, en correleren met de individuele mogelijkheid om een gezichtsveld te negeren (Händel et al, 2011;. Ter Huurne et al, 2013.). Theta-band oscillaties, frequenties tussen 4 en 7 Hz, worden meestal als een neuronale correlaat van de werkende hersenen gezien, bijvoorbeeld tijdens interne informatieverwerking (Kahana et al, 2001. Klimesch, 1999a). Eigenschappen van theta-oscillaties en verdere kenmerken van alfa-band oscillaties worden in meer detail in de afzonderlijke hoofdstukken, en meer in het algemeen in hoofdstuk 5.2, besproken.

Het belangrijkste doel van dit proefschrift is te onderzoeken hoe posterior alpha-oscillaties worden gemoduleerd door middel van aandacht, en of ze een causale rol spelen voor het mechanisme dat verantwoordelijk is voor het moduleren van aandacht. In het dagelijkse leven moeten wij onze aandacht voortdurend veranderen en flexibel aanpassen. Posterior alfa-band oscillaties worden verondersteld dat ze de toewijzing van de visueel-ruimtelijke aandacht geven (zie hoofdstuk 1.4).

In hoofdstuk 2 heb ik onderzocht of de mate van visuele aandacht verandert met de waarschijnlijkheid van een aanstaande stimulus op een onbewaakte plaats. Ik heb zowel gedrags performantie zoals de mate van alfa lateralisatie van proefpersonen gemeten. Deelnemers moesten hun geheime aandacht op één hemifield tonen totdat een stimulans verandering op de onbemande hemifield opgetreden was (dit benoemde ik een “schakelaar trial”). Als een schakelaar trial gedetecteerd was, moesten ze hun geheime aandacht naar het andere gezichtsveld overschakelen. Het is belangrijk om te vermelden dat onder de schakelaar trial een lineair kansmodel ligt (“schakelaar trial waarschijnlijkheid”). De kans op een stimulus nam toe. Deelnemers waren niet expliciet geïnformeerd over de schakelaar trial waarschijnlijkheid. Toch heeft mijn onderzoek laten zien dat de deelnemers in staat waren om de schakelaar trial waarschijnlijkheid tijdens het uitvoeren van de taak af te leiden. Dit vermogen verschilde tus-

sen individuen. Het belangrijkste was dat wanneer een deelnemer zijn posterieure alfa ritme volgens de switch trial waarschijnlijkheid moduleerde, hij beter in staat was een schakelaar stimulus te ontdekken als de schakelaar trial waarschijnlijkheid hoog was. Deze bevinding benadrukt het belang van het aanpassen van posterior alfa-band oscillaties naar onze directe omgeving voor optimale prestaties. Onlangs hebben Gould et al. (2011) aangetoond dat de mate van posterieure alfa lateralisatie gemoduleerd wordt volgens expliciete omgevings eigenschappen. Ik breidde deze vaststelling uit door te laten zien dat individuen ook in staat zijn om dit te doen voor omgevingseigenschappen die ze zelf moesten afleiden. Maar deze studie toonde ook aan dat een optimale aanpassing aan de omgeving niet door alle personen wordt bereikt.

Vervolgens onderzocht ik of de individuele mogelijkheid om de posterieure alfa-ritme te moduleren aangeleerd kan worden. Ik ontwikkelde een MEG brain-computer interface voor een geheime aandachtstaak met behulp van het posterieure alfa ritme. Met deze taak trainde ik deelnemers in vier sessies om hun alfa ritme te moduleren, terwijl lateraal gepresenteerde feedback hun tijdelijke niveau van alfa lateralisatie laten zien. In hoofdstuk 3 toonde ik aan dat de deelnemers kunnen leren om vrijwillig hun posterieure alpha lateralisatie te moduleren binnen een enkele sessie van minder dan tien minuten. Deelnemers worden aanzienlijk beter in het beheersen van hun alpha lateralisatie na de eerste sessie. Deze bevindingen tonen aan dat bewuste modulatie van posterior alfa lateralisatie mogelijk is en dat dit vermogen getraind kan worden. Bovendien stelde dit experiment dat alfa-oscillaties geschikt zijn om een brain-computer interface aan te sturen, omdat het een betrouwbaar stuursignaal is dat gemakkelijk en snel te leren is. Dit kan bijvoorbeeld een veelbelovend control signaal voor verlamde patiënten zijn. In tegenstelling tot de veel gebruikte ingebeelde beweging (Wolpaw et al., 1991) of visuele P300-paradigma (Farwell en Donchin, 1988), heeft geheime aandacht geen oogbewegingen nodig of het levendig voorstellen van spierbewegingen, die voor volledig locked-in patiënten niet geschikt zijn (Birbaumer en Cohen, 2007). Daarom zou het paradigma dat in hoofdstuk 3 gebruikt wordt een mogelijke alternatief zijn in die gevallen waar andere BCI paradigma's mislukken.

De studie in hoofdstuk 3 toonde ook aan dat huidige onderzoeken op het gebied van cognitieve neurowetenschappen kunnen helpen om betrouwbare controle signalen te identificeren ten behoeve van Brain-Computer Interfacing. Deze inzichten kunnen helpen om BCI stuursignalen in een natuurlijke omgeving in te bedden zoals bijvoorbeeld hier gedaan is: geheime aandacht moduleert het achterste alfa ritme, dus is het het natuurlijkste dat de deelnemers moeten leren om hun achterste alfa ritme te

regelen in een geheime aandachtsparadigma. Bovendien, gezien de sterke correlatie in geheime aandachtstaken tussen gedragsprestatie en de mate van alfa lateralisatie (zie bijvoorbeeld Kelly et al, 2009; Thut et al, 2006), onderzocht ik of training van de achterste alfa lateralisatie controle ook consequenties heeft voor gedragsverandering van de proefpersonen. Dit zou een causaal verband tussen de mate van posterior alpha lateralisatie en cognitieve prestaties tijdens geheime aandachtstaken aantonen. In hoofdstuk 4 bouwde ik een hypothese-gedreven brain computer interface met het doel om de effecten van BCI training, gebaseerd op alpha lateralisatie, op gedragsprestaties te onderzoeken. Veertig deelnemers krijgten ofwel feedback op hun achterste alfa ritme of ontvangen placebo feedback. Het belangrijkste is dat deelnemers alleen worden opgeleid om aandacht naar het linker of naar het rechter gezichtsveld te leggen. De belangrijkste bevinding was dat die proefpersonen die neurofeedback training gekregen hebben slechter geworden zijn in het aandacht geven aan de ongetrainde gezichtsveld. Dit was ook gerealiseerd door slechts 10 minuten neurofeedback training. De groep van deelnemers die schijnvertoning feedback kregen, lieten geen gedragsmodulatie door de eenzijdige training zien. Ook dit onderzoek suggereerde een oorzakelijk verband tussen alfa oscillaties en cognitieve prestaties bij geheime aandachtstaken. In de toekomst kunnen deze inzichten leiden tot interessante training paradigma's die kunnen dienen om aandachtstekorten te verminderen: we kunnen deelnemers trainen om een bepaald deel van de visuele input te negeren. Bijvoorbeeld, ADHD patiënten kunnen geen hoge alfa lateralisatie houden bij het bijwonen van het linker gezichtsveld (ter Huurne et al., 2013). In hoofdstuk 3 presenteerde ik bewijs dat de individuele mate om alfa lateralisatie te kunnen controleren getraind kan worden. Zo zullen ADHD patiënten misschien ook kunnen leren om een hoge mate van alfa lateralisatie te houden met behulp van dit paradigma. In combinatie met de bevindingen van hoofdstuk 4, zou men verwachten dat hun vermogen om afleidende informatie te negeren veberterd kan worden. In hoofdstuk 5 waren dit en worden aanverwante suggesties voor toekomstig onderzoek gepresenteerd. Verder vatte ik recent bewijs voor deze suggesties samen, en besprak aanverwante technieken zoals transcraniële magnetische stimulatie (TMS) en transcraniële gelijkstroom stimulatie (TCS). Verder besprak ik toepassingen voor verschillende doelgroepen, en beoordeelde ik kritisch praktische overwegingen van deze benaderingen. Tenslotte onderzocht ik in hoofdstuk 6 hoe corticostriatale netwerken met behulp van corticale oscillaties communiceren. Onlangs bleek dat het striatum rechtstreeks de mate van frontoparietale connectiviteit in visuele detectie taken moduleert (van Schouwenburg et al., 2013, 2010). Uit de bevindingen in hoofdstuk 2, hoofdstuk 3 en hoofdstuk 4 bleek dat de posterieure alfa-oscillaties onder

sterke top-down controle zijn, dwz gemoduleerd door andere hersengebieden die betrokken zijn bij taken rondom verwachting en bedoeling. Frontale gebieden rond de frontale oogvelden (FEF) en pariëtale regio's rond de intrapariëtale sulcus (IPS) zijn geïdentificeerd als top-down controle gebieden van posterieure alpha oscillaties door interventionele studies met behulp van TMS (Capotosto et al, 2012a, 2009; Sauseng et al, 2011). Zo zijn er aanwijzingen dat de mate van frontoparietale verbinding de verdeling van de achterste alpha oscillaties beïnvloedt, die op zijn beurt wordt gemoduleerd door het striatum. Daarom heb ik onderzoek gedaan, beschreven in hoofdstuk 6, naar de betrokkenheid van theta- en alfa-band oscillaties in striato-corticale en cortico-striatale interacties tijdens een geheime aandachtstaak. In samenwerking met het Academisch Medisch Centrum in Amsterdam, voerde ik een experiment uit bij patiënten met geïmplanteerde diepe hersen elektroden in het ventrale striatum (VS). Wij hebben tegelijk de intracraniële elektroden en hoofdhuid elektroden opgenomen en onderzocht hoe de VS en de neocortex met elkaar communiceren. Ik vond dat de VS samenwerkt met de frontale en pariëtale cortex in twee frequentie-banden: de theta-band en de alfa-band. In deze studie, toonde ik voor de eerste keer aan dat de menselijke corticostriatale netwerken gebruik maken van verschillende frequentiebanden voor bi-directionele communicatie. Verder heb ik de hypothese opgesteld dat het ventrale striatum fungeert als poortwachter tijdens aandachtstaken op soortgelijke wijze als de dorsale striatum dit doet tijdens werkgeheugentaken. Volgens deze hypothese, wordt informatie doorgegeven van het ventrale striatum naar de frontale (zie bijvoorbeeld Alexander et al., 1986) en pariëtale cortex (Saint-Cyr et al., 1990) in de theta-band, terwijl alfa-band oscillaties helpen om in afwachting van visuele informatie corticale verwerking te onderdrukken.

In dit proefschrift heb ik de individuele mogelijkheden om aandacht flexibel te moduleren onderzocht, of corticale alfa-band oscillaties te leren te controleren zijn, en of ze betrokken zijn bij corticostriatale communicatie. Ik heb gevonden dat het moduleren van de mate van posterieure alpha lateralisatie sterk verschilt tussen individuen, maar dat dit vermogen kan worden getraind door brain-computer interface training. Verder toonde ik dat succesvolle BCI training op het moduleren van de mate van alfa lateralisatie resulteert in een verandering in de gedragsprestaties. Hierdoor bevestigde ik het huidige bewijsmateriaal wat spreekt voor een causale rol van alfa oscillaties in cognitie. Ik besprak deze BCI aanpak, die ik hypothese-gedreven BCI (hdBCI) noemde, en besprak ik uitgebreid andere interventionele benaderingen. Tot slot, onderzocht ik hoe corticostriatale netwerken met elkaar interageren in de theta- en alfa-band. In navolging van deze reeks van studies zijn vele toekomstige onderzoeken op het ge-

bied van hypothese-gedreven brain-computer interfacing en aanverwante interventionele benaderingen mogelijk. In de toekomst kunnen deze paradigma's gebruikt worden om sterkere, functionele hypothesen in empirische studies te onderzoeken, en kunnen ze leiden tot nieuwe therapie mogelijkheden voor de behandeling van neurologische aandoeningen zoals ADHD.

Deutsche Zusammenfassung

Stell dir vor, dass du vor einer Ampel auf das grünes Licht wartest. Eine Ampel (siehe Abbildung 1) ist speziell auf die Aufmerksamkeitsprozesse im menschlichen Gehirn abgestimmt. Ein helles Licht verändert seine Farbe und Ort, und zieht deine Aufmerksamkeit in einer Bottom-Up Manier auf sich. Trotz der deutlichen Veränderung in deinem Sichtfeld, konzentrierst du deine Aufmerksamkeit ausschließlich auf die Ampel und ignorierst die Umgebung. Du könntest stattdessen natürlich auch zu dem roten Ferrari auf dem nahe gelegenen Parkplatz schauen. Wenn deine aktuelle oberste Priorität jedoch ist, dein Ziel so schnell wie möglich zu erreichen, dann ist es besser nicht von der Ampel abgelenkt zu sein und stattdessen bewusst deine Umgebung zu ignorieren, um deine Reaktionszeit zu optimieren, sobald das Licht auf grün springt. Dies nennt sich Top-Down Kontrolle der Aufmerksamkeit. Anders als bei der automatischen Bottom-up Aufmerksamkeit kann die Stärke der Top-down-Aufmerksamkeitskontrolle bewusst kontrolliert werden.

Abbildung 1: Eine Ample, die auf gelb gesprungen ist (oder auf Orange, wie es die Niederländer wahrnehmen, siehe Mitterer et al., 2009)

Bei visuell-räumlicher Aufmerksamkeit auf einen bestimmte Ort finden ruckartige Augenbewegungen (so genannte Sakkaden) zu genau dem Ort der Interesse statt. Auf diese Art und Weise wird die Mitte der Netzhaut, die Fovea, auf das fixiert, was dich am meisten interessiert: die Ampel. Bei Tageslicht ist die räumliche Auflösung in der Fovea am höchsten, daher ist

es sinnvoll auch das zu fixieren was dich am meisten interessiert (siehe Gazzaniga, 2008). Im Gegensatz zu dieser offenen, visuell-räumlichen Aufmerksamkeit, kannst du deine Aufmerksamkeit auch auf eine andere Stelle richten als dort, wo du du gerade hinschaust. Dies ist die so genannte verdeckte, visuell-räumliche Aufmerksamkeit, oder kurz, verdeckte Aufmerksamkeit (Posner, 1980). So könnte dein Lebenspartner während der Wartezeit auf das grüne Licht zum Beispiel ein Gespräch mit dir beginnen und dich bitten, ihn anzuschauen während ihr miteinander redet. Während du dies tust, könnte es aber nun sein,dass du insgeheim weiterhin auf die Ampel achtest anstatt zu deinem Partner, weil dir eine schnelle Reaktion auf das grüne Licht wichtiger ist als die Analyse der emotionalen Gesichtsausdrücke deines Partners.

Das visuelle System des menschlichen Gehirns ist relativ komplex. Der Haupteingang visueller Information sind die Augen. Sehzellen wandeln Photonen des einfallenden Lichts in elektrische Signale um, welche dann weiter zum Gehirn übertragen werden: die visuelle Information wird über das Chiasma an den seitlichen Kniehöcker (LGN) im Thalamus und von dort zum visuellen Kortex übertragen (siehe beispielsweise Gazzaniga, 2008), so wie zu anderen subkortikalen Regionen wie den Colliculus Superior (siehe zB Böhnke und Munoz, 2008). Das Chiasma kombiniert Informationen beider Augen gezielt auf Sichtfeld-spezifische Art und Weise: das linke Sichtfeld beider Augen wird vereint und durch den LGN an den rechten primären visuellen Kortex (Sehrinde) gesendet, und das rechte Sichtfeld beider Augen wird kombiniert und durch den LGN an den linken visuellen Kortex geschickt. Der visuelle Kortex ist die kortikale Haupteingangsschicht, wo visuelle Information verarbeitet und an höhere visuelle Bereiche des Gehirns gesendet. Die Sehrinde empfängt auch rezidivierende (wiederkehrende) Verbindungen höherer visueller Hinregion, wodurch die aktuelle visuelle Information mit dem Ergebnis der Verarbeitung dieser höheren visuellen Bereiche aktualisiert wird.

Neuronale Schwingungen repräsentieren grundlegenden Funktionen des menschlichen Gehirns, wobei unterschiedliche Frequenzbänder in verschiedenen, teilweise überlappende Prozesse involviert sind (Buzsáki und Draguhn, 2004). Diese Doktorarbeit beschreibt hauptsächlich Alpha-Band Schwingungen, die gewöhnlich als das Frequenzband zwischen 8 und 14 Hz festgelegt sind. Für eine lange Zeit dachte man, dass Alpha-Band Schwingungen den Ruhezustand des menschlichen Gehirns wiederspiegeln (Adrian und Matthews, 1934; Berger, 1929). Die aktuell vorherrschende Hypothese ist jedoch, dass Alpha-Band Schwingungen eine wichtige funktionelle Rolle durch die Hemmung von irrelevanten Hirnregionen einnehmen (Foxe und Snyder 2011; Fu et al, 2001;. Jensen und Mazaheri

2010; Klimesch, 1999a; Klimesch et al. 2007). Zum Beispiel wird bei verdeckten visuellen Aufmerksamkeitsprozessen das nicht-beachtete Sichtfeld durch den ipsilateralen occipito-parietalen Kortex verarbeitet und zeigt daher starke Alpha-Schwingungen. Dies spiegelt eine Funktionshemmung dieser Hirnregion dar. Im Gegensatz dazu zeigt die kontralaterale Hemisphäre schwache Alpha-Schwingungen, so dass sie funktionell disinhibitiert wird. Als Folge daher kann dort visuelle Information verarbeitet werden. Diese Disbalanz der Stärke der Alpha-Schwingungen zwischen des ipsi- und kontralateralen Kortex nennt man Alpha-Hemisphärische Lateralisierung, oder auch nur Alpha-Lateralisierung. Ein wichtiges Merkmal der Alpha-Schwingungen ist, dass sie antizipierend sind, was bedeutet, dass diese Alpha-Hemisphärische Lateralisierung bereits vor der eingehenden visuellen Stimulation existiert (Worden et al., 2000). Zahlreiche Studien haben eine starke Korrelation zwischen der Qualität der Verarbeitung eingehender visuelle Stimulationen und der Stärke der Alpha-Hemisphärische Lateralisierung gefunden (Kelly et al, 2009;.. Thut et al, 2006), was darauf hinweist, dass diese Alpha-Schwingungen zuverlässige neuronale Korrelate der visuell-räumlichen Aufmerksamkeit sind. Die Stärken der Alpha-Lateralisierung unterscheidet sich auch zwischen Individuen, und korreliert mit der individuellen Fähigkeit eines der beiden Sichtfelder zu ignorieren (Händel et al 2011;. Ter Huurne et al, 2013). Theta-Bandschwingungen, Frequenzen zwischen 4 und 7 Hz, werden üblicherweise als neuronales Korrelat des Arbeitsgedächtnisses gesehen, beispielsweise während der Verarbeitung interner Informationen (Kahana et al, 2001. Klimesch, 1999a). Weitere Eigenschaften der Theta-Schwingungen und andere Eigenschaften der Alpha-Band Schwingungen werden genauer in separaten Kapiteln, und ganz allgemein in Kapitel 5.2 besprochen.

Das Hauptziel dieser Arbeit war es zu untersuchen, wie Alpha-Schwingungen durch Aufmerksamkeit moduliert werden, und ob sie in einem kausalen Zusammenhang stehen zu dem Mechanismus im Gehirn der Aufmerksamkeit moduliert. Im Alltag müssen wir ständig unseren Aufmerksamkeitsfokus flexibel anpassen. Die generelle Hypothese ist, dass Alpha-Schwingungen die Aufteilung der visuell-räumlichen Aufmerksamkeit wiederspiegelt. (siehe Abschnitt 1.4). In Kapitel 2 habe ich geprüft, ob sich der Grad der visuellen Aufmerksamkeit mit der Wahrscheinlichkeit einer bevorstehenden visuellen Stimulation in einem nicht-beachteten Ort ändert. Ich habe sowohl die Verhaltensleistung als auch den Grad der Alpha Lateralisierung von Versuchspersonen gemessen. Die Teilnehmer mussten ihre verdeckte Aufmerksamkeit auf ein Sichtfeld richten, bis eine Stimulus Änderung im unbeachteten Sichtfeld stattfand ("Switch-

Stimulus"). Wenn die Versuchsperson ein Switch-Stimulus entdeckte, mussten sie ihre verdeckte Aufmerksamkeit auf eben dieses zuvor unbeachtete Sichtfeld richten. Hierbei ist es ist wichtig zu erwähnen, dass das Erscheinen eines Switch-Stimuluss einem linearen Wahrscheinlichkeitsmodell folgte ("Switch-Stimulus Wahrscheinlichkeit"). Die Wahrscheinlichkeit für ein Switch-Stimulus wurde höher mit längerer, verstrichener Zeit. Die Teilnehmer wurden nicht explizit über diese Switch-Stimulus Wahrscheinlichkeit informiert. Allerdings hat meine Forschung gezeigt, dass die Teilnehmer in der Lage waren, die Switch-Stimulus Wahrscheinlichkeit während der Ausführung der Aufgabe selber herzuleiten. Diese Fähigkeit unterschied sich zwischen einzelnen Individuen. Das wichtigste Ergebnis war, dass, wenn ein Teilnehmer seine Alpha-Schwingungen gemäß der Switch-Stimulus Wahrscheinlichkeit moduliert hatte, so war er auch besser einen Switch-Stimulus zu detektieren, wenn die Switch-Stimulus Wahrscheinlichkeit hoch war. Dieser Befund unterstreicht die Bedeutung der Anpassung der Alpha-Band Schwingungen an unsere unmittelbare Umgebung für eine optimale Verhaltensleistung. Kürzlich zeigte Gould (2011) et al., dass der Grad der Alpha-Lateralisierung gemäß expliziter Umgebungs-eigenschaften moduliert wird. Meine Arbeit erweiterte dieses Ergebnis insoweit, dass wir nun wissen, dass Alpha-Schwingungen auch angepasst werden, wenn Personen diese Umgebungseigenschaften selber herleiten müssen. Aber diese Studie zeigte auch, dass eine optimale Anpassung an die Umgebung nicht von allen Personen erreicht wird.

Ich habe daraufhin geprüft, ob die individuelle Fähigkeit Alpha-Schwingungen zu modulieren lernbar ist. Ich entwickelte eine MEG Gehirn-Computer-Schnittstelle für eine verdeckte Aufmerksamkeits-aufgabe mit Hilfe der Alpha-Lateralisierung. Ich trainierte die Teilnehmer in vier Sitzungen ihre Alpha-Schwingungen hiermit zu modulieren, während lateral präsentiertes Feedback ihre augenblickliche Alpha-Lateralisierung zeigte. In Kapitel 3 habe ich gezeigt, dass die Teilnehmer lernen konnten, ihre Alpha-Lateralisierung selbstständig zu modulieren binnen einer Sitzung von weniger als zehn Minuten. Die Teilnehmer hatten anschliessend eine deutlich bessere Kontrolle über ihre Alpha-Lateralisierung nach der ersten Sitzung. Dieses Ergebnis zeigt, dass eine bewusste Modulation der Alpha-Lateralisierung möglich ist, und dass diese Fähigkeit trainiert werden kann. Außerdem zeigte dieses Experiment, dass Alpha-Schwingungen geeignet sind, um eine Gehirn-Computer-Schnittstelle zu kontrollieren, da es ein zuverlässiges Kontrollsignal ist, das schnell und einfach zu erlernen ist. Beispielsweise kann dies ein vielversprechender Ansatz für Menschen mit Behinderungen darstellen. Im Gegensatz zu den meist benutzten imaginären Bewegung (Wolpaw et al., 1991) oder visuellen P300 Paradigmas

(Farwell und Donchin, 1988), erfordert verdeckte Aufmerksamkeit keine Augenbewegungen oder lebhafte Vorstellung von Muskelbewegungen, welche für vollständig Locked-In-Patienten nicht möglich sind (Birbaumer und Cohen, 2007). Daher ist das Paradigma aus Kapitel 3 eine vielversprechende Alternative, besonders in Fällen in denen andere Paradigmas in Gehirn-Computer-Schnittstellen scheitern.

Die Studie in Kapitel 3 zeigt auch, dass die neuesten Forschungseinsichten im Bereich der kognitiven Neurowissenschaften helfen können, zuverlässige Kontrollsignale für Gehirn-Computer Schnittstellen zu identifizieren. Diese Erkenntnis ermöglicht es, Kontrollsignale in einer natürlichen Umgebung zu verankern, so wie hier getan: Verdeckte Aufmerksamkeit moduliert auf natürliche Art und Weise Alpha-Schwingungen, daher ist es natürlich, dass die Teilnehmer lernen ihre Alpha-Schwingungen in einem verdeckten Aufmerksamkeit Paradigma zu modulieren. Angesichts der starken Korrelation, die in verdeckten Aufmerksamkeit Aufgaben zwischen Verhaltensleistung und dem Grad der Alpha Lateralisierung gefunden wurde (siehe zB Kelly et al, 2009; Thut et al, 2006), untersuchte ich, ob das Erlernen der Regulierung der Alpha-Lateralisierung dann auch Auswirkungen auf die Verhaltensleistung der Versuchsteilnehmer hat. Dieses würde einen kausalen Zusammenhang zwischen dem Grad der Alpha Lateralisierung und kognitiver Leistung bei verdeckten Aufmerksamkeitsaufgaben unter Beweis stellen. In Kapitel 4, baute ich solch eine hypothesengeleitete Gehirn-Computer-Schnittstelle, mit dem Ziel, die Auswirkungen des Alpha-Lateralisierungstrainings auf Verhaltensleistung zu untersuchen. Vierzig Teilnehmer wurde entweder echtes Feedback über ihre Alpha-Schwingungen gegeben oder sie empfingen Placebo Feedback. Der wichtigste Aspekt dieses Experimentes war es, dass die Teilnehmer während des Experiments ihre Aufmerksamkeit entweder auf das linke oder aber auf das rechte Sichtfeld richten durften. Die wichtigste Erkenntnis hier war, dass Probanden, die echtes Neurofeedback-Training erhielten, schlechter wurden um ihre Aufmerksamkeit auf das untrainierte Sichtfeld zu richten. Dies wurde erneut durch eine Sitzung von nur 10 Minuten erreicht. Die Gruppe der Teilnehmer, die Placebo Feedback erhielten zeigten hingegen keine Verhaltensmodulation durch das einseitige Sichtfeldtraining. Diese Studie legt nahe, dass es einen kausalen Zusammenhang zwischen Alpha-Schwingungen und kognitiver Leistungsfähigkeit gibt. In Zukunft könnte dies zu interessanten Trainingsparadigmen führen, um Aufmerksamkeitsdefizite zu reduzieren, indem wir Teilnehmer trainieren einen bestimmten Teil des visuellen Inputs zu ignorieren. So wurde zum Beispiel gezeigt, dass ADHS-Patienten keine starke Alpha-Lateralisierung aufrecht erhalten können, wenn sie ihre Aufmerksamkeit

auf das linke Sichtfeld richten (Ter Huurne et al., 2013). In Kapitel 3, präsentierte ich Beweise dafür, dass man lernen kann seine Alpha-Lateralisierung zu kontrollieren. Somit könnten ADHS-Patienten möglicherweise auch in der Lage sein mit diesem Paradigma zu lernen, ein hohes Maß an Alpha-Lateralisierung aufrechtzuerhalten. In Verbindung mit den Ergebnissen aus Kapitel 4 könnte man anschliessend erwarten, dass dies auch ihre Fähigkeit verbessern kann, ablenkende visuelle Stimuli zu ignorieren. In Kapitel 5 wurden diese und verwandte Forschungsempfehlungen diskutiert. Des Weiteren fasse ich aktuelle Forschungsbeweise zusammen, die diese Ideen unterstützen, und diskutiere verwandte Techniken wie transkranielle Magnetstimulation (TMS) und transkraniellen Gleichstromstimulation (TCS). Darüber hinaus diskutierte ich Anwendungen für unterschiedliche Zielgruppen, und beleuchtete praktische Überlegungen dieser Ansätze kritisch. Letztendlich untersuchte ich in Kapitel 6, wie kortikostriatale Netzwerke kortikaler Schwingunge nutzen um miteinander zu kommunizieren. Kürzlich wurde herausgefunden, dass das Striatum den Vernetzungsgrad zwischen frontoparietalen Hirngebieten während visueller Erkennungsaufgaben direkt moduliert (van Schouwenburg et al. 2013, 2010). Die Ergebnisse in Kapitel 2, Kapitel 3 und Kapitel 4 zeigten, dass Alpha-Schwingungen unter starker Top-Down-Kontrolle stehen, welche von Hirnregionen ausgehen muss, die in Erwartungs- und Absichtsprozessen involviert sind. Frontal Gebiete rund um die frontalen Augenfelder (FEF) und parietale Regionen wie der intraparietale Sulcus (IPS) wurden bereits als Top-Down-Kontrollregionen von Alpha-Schwingungen durch interventionelle Studien mit TMS identifiziert (Capotosto et al, 2012a, 2009, Sauseng, 2011). Zum Beispiel gibt es Hinweise darauf, dass der Grad der frontoparietalen Verbindung durch die Verteilung von Alpha-Schwingungen moduliert wird, welche ihrerseits durch das Striatum moduliert wird. Daher erforschte ich in Kapitel 6 die Beteiligung von Theta- und Alpha-Band Schwingungen in striato-kortikalen und kortiko-striatalen Interaktionen während einer verdeckten Aufmerksamkeitsaufgabe. In Zusammenarbeit mit dem akademisch-medizinischem Zentrum in Amsterdam (Academisch Medisch Centrum Amsterdam), führte ich ein Experiment mit Patienten aus, denen Hirnelektroden im ventralen Striatum (VS) zu medizinisch-therapeutischen Zwecken implantiert wurden. Wir haben gleichzeitig intrakranielle Elektroden und Kopfhaut-Elektroden aufgezeichnet und untersuchten, wie das VS und die Großhirnrinde miteinander interagieren. Ich fand heraus, dass das VS mit dem frontalen und parietalen Kortex in zwei Frequenzbändern interagiert: dem Theta-Band und dem Alpha-Band. In dieser Studie zeigte ich zum ersten Mal, das kortikostriatale Netzwerke beim Menschen verschiedene Frequenzbänder für die bidirektionale Kommunikation nutzen. Außerdem

habe ich die Hypothese aufgestellt, dass das ventrale Striatum als Pförtner während Aufmerksamkeitsaufgaben fungiert, und zwar auf eine ähnliche Weise wie das dorsale Striatum dies tut während Arbeitsgedächtnisaufgaben. Nach dieser Hypothese, wird Information vom ventralen Striatum zum frontalen Kortex im Theta-Band geleitet (siehe beispielsweise, Alexander et al., 1986), und parietalen Cortex (Saint-Cyr et al., 1990), während Alpha-Band Schwingungen dazu beitragen, die kortikale Verarbeitung visueller Information m Vorhinein zu unterdrücken.

In dieser Arbeit habe ich verschiedene Möglichkeiten untersucht, wie Aufmerksamkeit flexibel moduliert wird, ob kortikale Alpha-Band Schwingungen erlernt werden können, ob ihre Modulation zu erlernen ist, und ob sie in kortikostriataler Kommunikation beteiligt sind. Ich fand heraus, dass die Modulation der Stärke der Alpha-Lateralisierung stark zwischen einzelnen Individuen variiert, aber diese Fähigkeit durch die Nutzung von Gehirn-Computer-Schnittstelle trainiert werden kann. Ferner zeigte ich, dass solch ein erfolgreiches Training der Modulation der Alpha-Lateralisierung zu einer Änderung der Verhaltensleistung führt. Hiermit bestätigte ich die Hinweise anderer Studien, welche für eine kausale Rolle von Alpha-Schwingungen in kognitiven Prozessen sprechen. Ich diskutierte diesen Gehirn-Computer-Schnittstellen-Ansatz, den ich hypothesengeleitet nannte, und diskutierte ausgiebig ähnliche Interventionsansätze. Letztendlich untersuchte ich, wie kortikostriatale Netzwerke miteinander kommunizieren mit Hilfe von Alpha- und Theta-Band-Schwingungen. Aus dieser Untersuchungsreihe können in Zukunft viele anschließende Untersuchungen auf dem Gebiet der hypothesengeleitete Gehirn-Computer-Schnittstellen und verwandten Interventionsansätze folgen. So können solche Paradigmen verwendet werden, um aussagungskräftigere funktionelle Hypothesen in empirischen Studien zu untersuchen, und können zu neuen therapeutischen Maßnahmen für die Behandlung von neurologischen Erkrankungen wie zum Beispiel ADHS führen.

Acknowledgments

First of all, I would like to thank my dear supervisor Ole for his support over all these years. I always envied your unique Danish mix of enthusiasm close to euphoria, and thoroughness and depth when talking about science or personal matters. You taught me nearly everything I know about how to conduct good scientific research, what direction to think along, and how tackle tricky situations. I am sure I will value these lessons for the rest of my life, and hope to share them when I get older with the young ones. I had a great time in your lab and loads of fun. Thanks for having me!

Mathilde, Mathilde la bonne. I still remember the first encounter with you, when Ole asked me if I would be okay if you supervised me throughout my PhD (who am I to decide that?). It was a good and wise decision. You helped me so much and showed me a (the) way out when I got stuck, and you always had a big cup of optimism in your bag, paired with a good spoon of criticism and sharp eyes. But not only that, I am also happy that we could laugh together a lot in our meetings. Thanks for supervising me and teaching me critical thinking and to never be satisfied until the work is properly done! I hope we stay in touch. Merci beaucoup!

Robert and Jan-Mathijs, my dear, unofficial “second” supervisors. I cannot express how grateful I am that you took me into the FieldTrip hood. Thanks to you I now consider myself somewhat knowledgeable in signal processing and data analysis. I hope I paid back the time you spent on teaching me by squashing bugs and giving support to others. Most importantly, I hope you had an equally good time with me than I had with the two of you. It was always a pleasure when you or me dropped by for a chat, even if it was just for a “did you see *that* mail on the mailing list?”, or for some more serious, technical discussion. I hope to see you around, either for fun or for business (where’s the difference anyway?). And of course I will pass on the FieldTrip spirit to future generations!

Roshan, thanks for the nice time with you in the past four years. I always liked the occasional meetings with you, starting off with a short personal chat, followed by an in-depth discussion, which was falling somewhere between data analyses and scientific hypotheses. I always had the feeling that there is so much more to learn from you, and the so many other ways to think about my data and results. I really enjoyed the freshness of this new perspective. I would also like to thank your group members who supported me during my time at the Donders. Martine, thanks for the introduction to the striatum and basal ganglia, and your support especially during the first weeks as a PhD student. I hope you realized by now that I am not the only one reading your papers :) Also thanks for the nice

dinner in San Francisco. Sean, thanks a lot for your patience with me as an fMRI-newbie. I am not sure in how many ways I phrased the same questions over and over again, until I finally understood what I should have been doing. I hope you never realized that :) I hope you will never lose your jolliness and uniqueness.

Speaking of fMRI, Rene, Mr. number three of my four-people fMRI support group. Although I felt a bit overwhelmed initially when discussing fMRI and EEG experimental timings and synchronization, you helped me a lot in understanding the why and how. I also always enjoyed your sense of humor quite a lot and the late evening scan sessions. Thanks for all the fun and support.

Johanna, my final fMRI support. Thanks for taking your time in helping me with GLMs and regressions. And also I had a great time in our evening Skype-meetings (despite some literal blackouts), the discussions about future applications of our research and the fun way to work together. I hope the outcome of this work will be useful in future for both of us. Good luck on the island over there!

Ali B., Mr. senior author. Thanks for the fruitful discussions and nice chats about all aspects of life and science. I always envied you for your will to struggle through the jungle of academia despite all those obstacles. I am confident that your hard work will pay off. Maybe learn some sarcasm along the way, might never hurt… :)

Thanks to my collaborators in Amsterdam. Damiaan, thanks for enabling this project and for the support during the project. Ruud, thanks for all the interesting discussions we had a about analysis techniques, the weirdness of the data and our results, followed by sudden enlightments. I am curious what problems the world of research and science will bring us next, but I am confident that we could help each other out to be best prepared for whatever is coming next.

Dear Yuka-san, what a pleasure it was to work with you. Despite the long distance and living in different timezones, it seemed like your circadian cycle was always still synced with the European one and that we could always resolve any problem within a couple of hours. Always keep up your humor and happy mood; I am sure it always makes life easier, also when life is not so sugoi.

A very special thanks to all the members of the neuronal oscillations group! This thanks goes out to all the past and present members, which are (in no particular order) Ali M., Saskia, Stephen, Verena, Freek, Esther, Yuka, Avgis, Jan, Ali B., Niels, Mathilde, Rene, Til, Johanna, Eelke, Diego, Tom, Haiteng, Marieke, Lisa, Madelon, Bart, Jim, Maarten, Rocio, Tineke, Tzvetan, Sophie and Linda. It was an awesome experience to work with you, discuss science and other matters with you, laugh together (and drink together). It was a very stimulating experience,

and I know that it will not happen often to work together with only smart, nice and tolerable guys. It was a real honor. I hope we all stay in touch somehow and will see each other throughout our journeys through life. Also thanks to all the interns who only stayed for a few months. Especially I have to name Wouter here. I hope we will see each other again, and maybe work together one day. It was a pleasure supervising you.

I would also like to thank my second Donders family, the Fieldtrip team. Although strongly overlapping with the neuronal oscillations group, in addition there were Lilla, Roemer, Nietzsche and Arjen, and of course Robert and Jan-Mathijs. I will for sure miss the stimulating FieldTrip meetings, both the official ones and the inofficial ones in the evening. It was a real pleasure working with all of you on this project. I will do my best to keep on contributing. Eelke and Arjen, thanks for the awesome work during the workshops we gave, it was a great experience preparing the workshops with you and teaching others the FieldTrip way.

Thanks to my Donders roomies from 2.32: Ana, Katinka, Monique, Raimon, and Lisa. It was great fun sharing an office with you and getting a welcome distraction every once in a while. Also thanks to the great few weeks I spent in my new office 2.262 with Niels, Catalina, Monja and Jacob. Thanks for welcoming me in your small club, it was a nice time! Also thanks to the awesome support staff at the Donders, the TG, the secretarians, etc.. Without you, all our work would not be possible!

I would also like to thanks all those who supported and supervised me along the way to where I am now. Peter, Rutger, Jason and the whole CAI team, thanks for the nice time during my Master thesis. It was great working together with you. I would also like to thank Kevin, who has taught me the essence of writing nearly 10 years ago, anonymously over the internet. Thanks for your thoroughness, kindness and patience back then! It is a pity that we will most likely never meet in real life. Holger and Asifa, thanks for taking me as an intern when I was a little, second year Bachelor student. It was my first trip into the academic research world, and enabled me to walk my way up until here (and thanks to Peter for convincing you to take me!). Also thanks to my supervisors and teachers during my Bachelors, especially to Ronald and Ralf. You taught me well and showed me that working in academia is both fun and interesting. Also thanks to my Maastricht roommates, Hennes, Niels, Micha, Daniel and Fabian. It was great living with you and having you as a small little family. Special thanks to Hennes and Micha for learning together with me for exams and showing me that everything is possible. Cecilia, Peter, Marijn and Goedie, thanks for the nice time during my Master's (and beyond). It was great learning and discussing science with you, and it is great having you as friends.

There are many, many more to name here (e.g. Hugo and the Donders: Ali M., Stephen, Miriam, and of course Hugo). Please excuse me if I did not mention specifically you, but of course I am most grateful to especially you! Also thanks to all reviewers, which made the past four years a hard but instructive trip. Just not you, reviewer 2 - I despise you.

A special thanks to my dear paranimphs Jim and Lisa. You are not only standing by my side during my defense, but I especially value your openness, kindness and humor as friends. Thanks for all your help.

Another special thanks to the whole Artinis crowd, who gave me a warm welcome in my first “real” job. Willy and Roeland, thanks for taking me, I think it was a wise decision :) Marianne, Marco, Rosita, Ruby, Wout, Fransisco, Luc, Arian, Jaap, Berry, Henny and Tim, thanks for the great fun and the nice work atmosphere we are having. This makes even Mondays a bearable day each week. Ruby, thanks for all your help with the layout! I believe we can achieve great things in near future and I am really looking forward to this!

Vielen Dank auch an alle meine Freunde, die mich allzeit unterstützt haben. Danke Eric, Andre und Karina, Thomas und Christina, Holgi, Denise und Armin, Florian und Justine und James, Eva und Ben und Lena, Jim und Michelle und Dante, die Nilaihah Gang Stevie und Joni (und Makkus und Koch), Döll, Anika und Malte, Romy und Oomen. Und auch Danke an alle anderen die ich aus Platzgründen hier leider nicht nenne – oder aus Versehen vergessen habe. Eure Freundschaft und der gemeinsame Spaß haben mich unwahrscheinlich gefestigt!

Natürlich vielen Dank an meine Familie, meine Eltern Uwe und Renate, die mir vertraut haben und mich jederzeit unterstützt haben ohne mich unter Druck zu setzen. Danke an meinen Bruder Markus, der mir immer ein gutes Vorbild war – oder ein schlechtes, was mir wiederrum zeigte wie man es besser macht :) Auch vielen Dank an meine „erweiterte“ Familie, Werner, Marion, Judith, Reiner, Heinz, Andre und Karina. Danke, dass wir zusammen lachen und uns jederzeit unterstützen.

Anne, vielen Dank für die schönen letzten 9 Jahre. Ich weiß nicht wer oder wo ich ohne dich wäre, aber ich denke nicht, dass es besser oder schöner hätte sein können. Ich liebe dich – für immer.

Publication List

Okazaki, Y.*, Horschig, J.M.*, Luther, L., Oostenveld, R., Murakami, I., Jensen, O. (2015), Real-time MEG neurofeedback training of posterior alpha activity modulates subsequent visual detection performance. NeuroImage 107, 323-332. doi:10.1016/j.neuroimage.2014.12.014

Horschig, J.M., Oosterheert, W., Oostenveld, R., Jensen, O. (2014) Modulation of posterior alpha activity by spatial attention allows for controlling a continuous brain-computer interface, Brain Topography. doi:10.1007/s10548-014-0401-7

Horschig, J.M., Zumer, J.M., Bahramisharif, A. (2014) Hypothesis-driven methods to augment human cognition by optimizing cortical oscillations, Frontiers in Systems Neuroscience 8, 119. doi:10.3389/fnsys.2014.00119

Horschig, J.M., Jensen, O, van Schouwenburg, M.R., Cools, R, Bonnefond, M (2014) Alpha activity reflects individual abilities to adapt to the environment. NeuroImage 89, 235-243. doi:10.1016/j.neuroimage.2013.12.018

Mitterer, H., Horschig, J.M., Müsseler, J., Majid, A. (2009) The influence of memory on perception: It's not what things look like, it's what you call them. J. Exp. Psychol. Learn. Mem. Cogn. 35, 1557–1562. doi:10.1037/a0017019

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In preparation

Horschig, J.M., Smolders, R., Bonnefond, M., Schoffelen, J., van den Munckhof, P., Schuurman, P.R., Cools, R., Denys, D., Jensen, O. *(submitted)*, Directed communication between nucleus accumbens and neocortex in humans is differentially supported by synchronization in the theta and alpha band

Curriculum Vitae

Jörn Martin Horschig was born on 30 January 1985 in Kleve, Germany. After finishing high school and military service, he obtained a Bachelor degree cum laude in "Knowledge Engineering | Computer Science" from Maastricht University, Netherlands, in 2008. During the Bachelor programme, Jörn conducted a research internship at the Max-Planck Institute for Psycholinguistic in Nijmegen, the Netherlands, under supversion of Dr. Holger Mitterer and Dr. Asifa Majid. His Bachelor thesis was on automatic detection of burst-suppression patterns in the EEG of neonates using wavelets under supervision of Prof. Ralf Peeters and Dr. Jos Reulen. In 2010, he graduated with honours (bene meritum) from the prestigious Master programme "Cognitive Neuroscience" of Radboud University Nijmegen, Netherlands. In his Master thesis, Jörn investigated the "free BCI" approach, the possibility to control a brain-computer interface (BCI) without predefined tasks or instructions, supervised by Prof. Peter Desain and Dr. Rutger Vlek. Thereafter, Jörn became a PhD student in Prof. Ole Jensen's "Neuronal Oscillations" group at the Donders Institute for Brain, Cognition and Behavior of Radboud University Nijmegen, Netherlands. During his time as a PhD student, Jörn investigated the functional role, flexibility and trainability of posterior alpha oscillations, partly in collaboration with Prof. Roshan Cools from the Donders Institute and Prof. Damiaan Denys from Amsterdam Medical Centre. The results of these investigations are described in this thesis. During his time at the Donders Institute, he was part of the core development team of FieldTrip, an open-source Matlab toolbox for electrophysiological data analysis, managed by Dr. Robert Oostenveld and Dr. Jan-Mathijs Schoffelen. In 2014, he finished his PhD thesis and became a postdoctoral scientist at the Donders Institute in Ole Jensen's lab, while he also started working as a software engineer at Artinis Medical Systems, a small company located in Elst, Netherlands, creating near-infrared spectroscopy devices measuring blood oxygenation, which are widely used in the fields of neuroscience and sports science. Since January 2015, Jörn is working full-time at Artinis Medical Systems.

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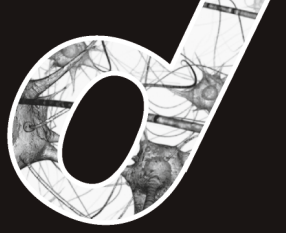

ISBN 978-94-6284-020-1

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